



Clinical trial results:

A Phase 3, randomized, double-blind efficacy and safety study comparing SAR442168 to teriflunomide (Aubagio®) in participants with relapsing forms of multiple sclerosis (GEMINI 1)

Summary

| | |
|--------------------------|----------------------------------|
| EudraCT number | 2020-000637-41 |
| Trial protocol | DE BG CZ FI SE AT DK LT PL IT RO |
| Global end of trial date | 15 July 2024 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 06 July 2025 |
| First version publication date | 06 July 2025 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | EFC16033 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-----------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04410978 |
| WHO universal trial number (UTN) | U1111-1238-1418 |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Sanofi aventis recherche & développement |
| Sponsor organisation address | 450 Water Street, Cambridge, Massachusetts, United States, 02141 |
| Public contact | Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com |
| Scientific contact | Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.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 | 30 August 2024 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 15 July 2024 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To assess efficacy of daily tolebrutinib compared to a daily dose of 14 milligrams (mg) teriflunomide (Aubagio) measured by the annualized adjudicated relapse rate (ARR) in participants with relapsing forms of multiple sclerosis (MS).

Protection of trial subjects:

Participants were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the participant and considering the local culture. During the course of the trial, participants were provided with individual participant cards indicating the nature of the trial the participant is participating, contact details and any information needed in the event of a medical emergency.

Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 30 June 2020 |
| 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 | Austria: 3 |
| Country: Number of subjects enrolled | Belarus: 15 |
| Country: Number of subjects enrolled | Bulgaria: 61 |
| Country: Number of subjects enrolled | Canada: 13 |
| Country: Number of subjects enrolled | China: 118 |
| Country: Number of subjects enrolled | Czechia: 70 |
| Country: Number of subjects enrolled | Denmark: 8 |
| Country: Number of subjects enrolled | Estonia: 26 |
| Country: Number of subjects enrolled | Finland: 4 |
| Country: Number of subjects enrolled | Germany: 10 |
| Country: Number of subjects enrolled | Hong Kong: 4 |
| Country: Number of subjects enrolled | Italy: 43 |
| Country: Number of subjects enrolled | Japan: 18 |
| Country: Number of subjects enrolled | Lithuania: 21 |
| Country: Number of subjects enrolled | Mexico: 24 |
| Country: Number of subjects enrolled | Poland: 81 |

| | |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Romania: 25 |
| Country: Number of subjects enrolled | Russian Federation: 106 |
| Country: Number of subjects enrolled | Spain: 58 |
| Country: Number of subjects enrolled | Sweden: 7 |
| Country: Number of subjects enrolled | Taiwan: 4 |
| Country: Number of subjects enrolled | Türkiye: 37 |
| Country: Number of subjects enrolled | Ukraine: 132 |
| Country: Number of subjects enrolled | United States: 86 |
| Worldwide total number of subjects | 974 |
| EEA total number of subjects | 417 |

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) | 974 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

A total of 1152 participants were screened from 30-Jun-2020 to 04-Aug-2022, of which 178 were screen failures. Screen failures were mainly due to not meeting eligibility criteria.

Pre-assignment

Screening details:

A total of 974 participants were randomized in this study in a 1:1 ratio to either teriflunomide 14 mg or tolebrutinib 60 mg group. This was an event-driven (6-month confirmed disability worsening [CDW]) trial with a variable treatment duration (end-of-study [EOS] duration: up to approximately 48 months).

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, Monitor, Carer, Assessor |

Arms

| | |
|------------------------------|---------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Teriflunomide 14 mg |

Arm description:

Participants received teriflunomide 14 mg tablet orally once daily (QD) along with a placebo matched to tolebrutinib orally QD up to approximately 47 months.

| | |
|--|--------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Teriflunomide |
| Investigational medicinal product code | |
| Other name | Aubagio |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Teriflunomide 14 mg was administered as a tablet orally QD up to approximately 47 months.

| | |
|--|--------------------|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo matched to tolebrutinib was administered as a tablet orally QD up to approximately 47 months.

| | |
|------------------|--------------------|
| Arm title | Tolebrutinib 60 mg |
|------------------|--------------------|

Arm description:

Participants received tolebrutinib 60 mg tablet orally QD along with a placebo matched to teriflunomide orally QD up to approximately 48 months.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo matched to teriflunomide was administered as a tablet orally QD up to approximately 48

months.

| | |
|--|--------------------|
| Investigational medicinal product name | Tolebrutinib |
| Investigational medicinal product code | SAR442168 |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Tolebrutinib 60 mg was administered as a tablet orally QD up to approximately 48 months.

| Number of subjects in period 1 | Teriflunomide 14 mg | Tolebrutinib 60 mg |
|---------------------------------------|---------------------|--------------------|
| Started | 488 | 486 |
| Completed | 415 | 409 |
| Not completed | 73 | 77 |
| Consent withdrawn by subject | 64 | 66 |
| Poor compliance to protocol | 2 | 4 |
| Unspecified | 6 | 7 |
| Missing study status | 1 | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | Teriflunomide 14 mg |
|-----------------------|---------------------|

Reporting group description:

Participants received teriflunomide 14 mg tablet orally once daily (QD) along with a placebo matched to tolebrutinib orally QD up to approximately 47 months.

| | |
|-----------------------|--------------------|
| Reporting group title | Tolebrutinib 60 mg |
|-----------------------|--------------------|

Reporting group description:

Participants received tolebrutinib 60 mg tablet orally QD along with a placebo matched to teriflunomide orally QD up to approximately 48 months.

| Reporting group values | Teriflunomide 14 mg | Tolebrutinib 60 mg | Total |
|------------------------|---------------------|--------------------|-------|
| Number of subjects | 488 | 486 | 974 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|---|-------|-------|-----|
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 36.6 | 36.8 | |
| standard deviation | ± 9.4 | ± 9.0 | - |
| Sex: Female, Male | | | |
| Units: participants | | | |
| Female | 325 | 334 | 659 |
| Male | 163 | 152 | 315 |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 3 | 6 | 9 |
| Asian | 67 | 78 | 145 |
| Native Hawaiian or Other Pacific Islander | 0 | 1 | 1 |
| Black or African American | 10 | 4 | 14 |
| White | 406 | 395 | 801 |
| More than one race | 1 | 1 | 2 |
| Unknown or Not Reported | 1 | 1 | 2 |

End points

End points reporting groups

| | |
|---|---------------------|
| Reporting group title | Teriflunomide 14 mg |
| Reporting group description: Participants received teriflunomide 14 mg tablet orally once daily (QD) along with a placebo matched to tolebrutinib orally QD up to approximately 47 months. | |
| Reporting group title | Tolebrutinib 60 mg |
| Reporting group description: Participants received tolebrutinib 60 mg tablet orally QD along with a placebo matched to teriflunomide orally QD up to approximately 48 months. | |

Primary: Annualized Relapse Rate as Assessed by Confirmed Protocol-defined Adjudicated Relapses

| | |
|---|--|
| End point title | Annualized Relapse Rate as Assessed by Confirmed Protocol-defined Adjudicated Relapses |
| End point description: The MS relapse was defined as a monophasic, acute or subacute onset of new neurological symptoms or worsening of previous neurological symptoms with an objective change on neurological examination. Symptoms were attributable to MS, lasted for ≥ 24 hours with or without recovery, present at normal body temperature, and preceded by ≥ 30 days of clinical stability. The intent-to-treat (ITT) population included all randomized participants according to the intervention group allocated by the randomization, irrespective of the study intervention received. | |
| End point type | Primary |
| End point timeframe: Baseline (Day 1) to approximately 48 months | |

| End point values | Teriflunomide 14 mg | Tolebrutinib 60 mg | | |
|--------------------------------------|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 488 | 486 | | |
| Units: relapses per participant year | | | | |
| number (confidence interval 95%) | 0.122 (0.100 to 0.150) | 0.130 (0.108 to 0.156) | | |

Statistical analyses

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|--|--|
| Statistical analysis title | Annualized Relapse Rate |
| Statistical analysis description: Analysis was performed using negative binomial model with number of adjudicated relapses onset between randomization date and EOS date as the response variable, treatment group, Gadolinium (Gd)-enhancing T1 lesions at baseline (presence, absence), expanded disability status scale (EDSS) strata (<4 , ≥ 4) and geographic region (United States [US], non-US) as covariates, and log transformed observation duration as the offset variable. | |
| Comparison groups | Teriflunomide 14 mg v Tolebrutinib 60 mg |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 974 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[1] |
| P-value | = 0.6691 ^[2] |
| Method | Chi-squared |
| Parameter estimate | Relative risk |
| Point estimate | 1.061 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.808 |
| upper limit | 1.393 |

Notes:

[1] - A hierarchical testing procedure was used to control the overall type I error.

[2] - Threshold for significance at 2-sided 0.05 level.

Secondary: Time to Onset of 6-Month Confirmed Disability Worsening as Assessed by Expanded Disability Status Scale

| | |
|-----------------|---|
| End point title | Time to Onset of 6-Month Confirmed Disability Worsening as Assessed by Expanded Disability Status Scale |
|-----------------|---|

End point description:

The EDSS was a disability scale that assessed the following 7 functional domains: visual, brainstem, pyramidal [motor], cerebellar [coordination], sensory, cerebral, and bowel/bladder. The total EDSS score ranged from 0 (normal) to 10 (death due to MS), increasing in increments of 0.5 points. Higher scores indicated increased disability. Time to onset of 6-month CDW was defined as the time from randomization to the onset of a confirmed, sustained increase from baseline in EDSS score (of ≥ 1.5 points when the baseline score was 0, of ≥ 1.0 point when the baseline score was 0.5 to ≤ 5.5 , of ≥ 0.5 points when the baseline EDSS score was > 5.5) over at least 6 months that was not attributable to another etiology. The ITT population included all randomized participants according to the intervention group allocated by the randomization, irrespective of the study intervention received.

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

End point timeframe:

Baseline (Day 1) to approximately 48 months

| End point values | Teriflunomide 14 mg | Tolebrutinib 60 mg | | |
|-------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 488 | 486 | | |
| Units: months | | | | |
| median (full range (min-max)) | 17.97 (2.9 to 33.9) | 15.38 (2.6 to 36.8) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Time to Onset of 6-Month CDW as Assessed by EDSS |
|----------------------------|--|

Statistical analysis description:

Analysis was performed using Cox proportional-hazards model with robust variance estimation. Covariates were treatment group, Gd-enhancing T1 lesions at baseline (presence, absence), EDSS strata (< 4 , ≥ 4), geographic region (US, non-US).

| | |
|-------------------|--|
| Comparison groups | Teriflunomide 14 mg v Tolebrutinib 60 mg |
|-------------------|--|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 974 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[3] |
| P-value | = 0.4888 ^[4] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.85 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.565 |
| upper limit | 1.278 |

Notes:

[3] - A hierarchical testing procedure was used to control the overall type I error.

[4] - Derived from log-rank test with stratification of EDSS strata (<4, >=4), geographic region (US, non-US).

Secondary: Time to Onset of 3-Month Confirmed Disability Worsening as Assessed by Expanded Disability Status Scale

| | |
|-----------------|---|
| End point title | Time to Onset of 3-Month Confirmed Disability Worsening as Assessed by Expanded Disability Status Scale |
|-----------------|---|

End point description:

The EDSS was a disability scale that assessed the following 7 functional domains: visual, brainstem, pyramidal [motor], cerebellar [coordination], sensory, cerebral, and bowel/bladder. The total EDSS score ranged from 0 (normal) to 10 (death due to MS), increasing in increments of 0.5 points. Higher scores indicated increased disability. Time to onset of 3-month CDW was defined as the time from randomization to the onset of a confirmed, sustained increase from baseline in EDSS score (of >=1.5 points when the baseline score was 0, of >=1.0 point when the baseline score was 0.5 to <=5.5, of >=0.5 points when the baseline EDSS score was >5.5) over at least 3 months that was not attributable to another etiology. The ITT population included all randomized participants according to the intervention group allocated by the randomization, irrespective of the study intervention received.

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

End point timeframe:

Baseline (Day 1) to approximately 48 months

| End point values | Teriflunomide 14 mg | Tolebrutinib 60 mg | | |
|-------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 488 | 486 | | |
| Units: months | | | | |
| median (full range (min-max)) | 17.96 (2.9 to 39.3) | 14.93 (0.2 to 41.0) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Time to Onset of 3-Month CDW as Assessed by EDSS |
|----------------------------|--|

Statistical analysis description:

Analysis was performed using Cox proportional-hazards model with robust variance estimation. Covariates were treatment group, Gd-enhancing T1 lesions at baseline (presence, absence), EDSS strata (<4, >=4), geographic region (US, non-US).

| | |
|-------------------|--|
| Comparison groups | Teriflunomide 14 mg v Tolebrutinib 60 mg |
|-------------------|--|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 974 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[5] |
| P-value | = 0.2991 ^[6] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.819 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.582 |
| upper limit | 1.151 |

Notes:

[5] - A hierarchical testing procedure was used to control the overall type I error.

[6] - Derived from log-rank test with stratification of EDSS strata (<4, >=4), geographic region (US, non-US).

Secondary: Mean Number of new and/or Enlarging T2-Hyperintense Lesions per Year

| | |
|-----------------|--|
| End point title | Mean Number of new and/or Enlarging T2-Hyperintense Lesions per Year |
|-----------------|--|

End point description:

Magnetic resonance imaging (MRI) of the brain was performed to identify number of new and/or enlarging T2-hyperintense lesions defined as the sum of the individual number of new and/or enlarging T2 lesions starting from baseline up to and including the EOS visit. The ITT population included all randomized participants according to the intervention group allocated by the randomization, irrespective of the study intervention received.

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

End point timeframe:

Baseline (Day 1) to approximately 48 months

| End point values | Teriflunomide 14 mg | Tolebrutinib 60 mg | | |
|---|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 488 | 486 | | |
| Units: number of new and or enlarging T2lesions | | | | |
| arithmetic mean (confidence interval 95%) | 5.175 (4.447 to 6.024) | 5.611 (4.826 to 6.524) | | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Number of new/Enlarging T2-Hyperintense Lesions |
|----------------------------|---|

Statistical analysis description:

Analysis was performed using negative binomial model with the number of new and/or enlarging T2-hyperintense lesions between randomization date and EOS date as the response variable, treatment group, baseline T2-hyperintense lesion count, EDSS strata (<4, >=4) and geographic region (US, non-US) as covariates, and log transformed observation duration as the offset variable.

| | |
|-------------------|--|
| Comparison groups | Teriflunomide 14 mg v Tolebrutinib 60 mg |
|-------------------|--|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 974 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[7] |
| P-value | = 0.4575 |
| Method | Chi-squared |
| Parameter estimate | Relative risk |
| Point estimate | 1.084 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.876 |
| upper limit | 1.342 |

Notes:

[7] - A hierarchical testing procedure was used to control the overall type I error.

Secondary: Mean Number of new Gadolinium-Enhancing T1-Hyperintense Lesions per Scan

| | |
|-----------------|--|
| End point title | Mean Number of new Gadolinium-Enhancing T1-Hyperintense Lesions per Scan |
|-----------------|--|

End point description:

MRI of the brain was performed to identify number of new Gd-enhancing T1-hyperintense lesions defined as the sum of the individual number of new Gd- enhancing T1-hyperintense lesions starting from baseline up to and including the EOS visit. The ITT population included all randomized participants according to the intervention group allocated by the randomization, irrespective of the study intervention received.

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

End point timeframe:

Baseline (Day 1) to approximately 48 months

| End point values | Teriflunomide 14 mg | Tolebrutinib 60 mg | | |
|--|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 488 | 486 | | |
| Units: number of new Gd-enhancing T1 lesions | | | | |
| arithmetic mean (confidence interval 95%) | 0.285 (0.221 to 0.367) | 0.530 (0.439 to 0.641) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Number of new Gd-Enhancing T1-Hyperintense Lesions |
|----------------------------|--|

Statistical analysis description:

Analysis was performed using negative binomial model with the number of new Gd-enhancing T1-hyperintense lesions between randomization date and EOS date as the response variable, treatment group, Gd-enhancing T1 lesions at baseline (presence, absence), EDSS strata (<4, >=4) and geographic region (US, non-US) as covariates, and log transformed number of MRI scans as the offset variable.

| | |
|-------------------|--|
| Comparison groups | Teriflunomide 14 mg v Tolebrutinib 60 mg |
|-------------------|--|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 974 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[8] |
| P-value | = 0.0001 |
| Method | Chi-squared |
| Parameter estimate | Relative risk |
| Point estimate | 1.86 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.358 |
| upper limit | 2.548 |

Notes:

[8] - A hierarchical testing procedure was used to control the overall type I error.

Secondary: Change From Baseline in Cognitive Function as Assessed by the Symbol Digit Modalities Test (SDMT) at EOS

| | |
|-----------------|--|
| End point title | Change From Baseline in Cognitive Function as Assessed by the Symbol Digit Modalities Test (SDMT) at EOS |
|-----------------|--|

End point description:

The SDMT was used to assess processing speed, divided attention, visual scanning, tracking and motor speed. It involved a simple substitution task using a reference key. The number of correct substitutions and number of items completed within a 90 second interval (maximum 110 seconds) were recorded. A decrease of 4 points from baseline on the SDMT was considered meaningful worsening. The score was the number of correctly coded items from 0-110 in 90 seconds; higher scores indicating a better outcome. Baseline was defined as the last available value prior to the first dose of study intervention. Analysis was performed on the ITT population. Only participants with data collected at specified timepoints are reported.

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

End point timeframe:

Baseline (Day 1) to EOS (up to approximately 48 months)

| End point values | Teriflunomide 14 mg | Tolebrutinib 60 mg | | |
|-------------------------------------|---------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 396 | 393 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | 0.329 (± 0.0318) | 0.364 (± 0.0318) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Change From Baseline in Cognitive Function: SDMT |
|----------------------------|--|

Statistical analysis description:

Covariates in the mixed-effect model with repeated measures (MMRM) were treatment group, EDSS strata (<4, ≥4), geographic region (US, non-US), visit, treatment by visit interaction, baseline value, and baseline value-by-visit interaction.

| | |
|-------------------|--|
| Comparison groups | Teriflunomide 14 mg v Tolebrutinib 60 mg |
|-------------------|--|

| | |
|---|-----------------------------------|
| Number of subjects included in analysis | 789 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[9] |
| P-value | = 0.432 |
| Method | MMRM |
| Parameter estimate | Least square (LS) mean difference |
| Point estimate | 0.035 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.053 |
| upper limit | 0.124 |

Notes:

[9] - A hierarchical testing procedure was used to control the overall type I error.

Secondary: Change From Baseline in Cognitive Function as Assessed by the California Verbal Learning Test Second Edition (CVLT-II) at EOS

| | |
|-----------------|---|
| End point title | Change From Baseline in Cognitive Function as Assessed by the California Verbal Learning Test Second Edition (CVLT-II) at EOS |
|-----------------|---|

End point description:

The CVLT-II was a verbal learning and memory test consisting of recall and recognition of a list of 16 words. For each assessment, 5 trials were completed. Total Correct Recall Trials 1-5 was scaled to a normalized T-score metric, which had a mean of 50 and standard deviation of 10, the maximum possible score was 80 and a minimum was 0. Higher values indicated improved cognitive function. Baseline was defined as the last available value prior to the first dose of study intervention. The ITT population included all randomized participants according to the intervention group allocated by the randomization, irrespective of the study intervention received. Only participants with data collected at specified timepoints are reported.

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

End point timeframe:

Baseline (Day 1) to EOS (up to approximately 48 months)

| End point values | Teriflunomide 14 mg | Tolebrutinib 60 mg | | |
|-------------------------------------|---------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 391 | 390 | | |
| Units: T-score | | | | |
| least squares mean (standard error) | 15.827 (± 0.7241) | 17.700 (± 0.7236) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Change From Baseline in Cognitive Function:CVLT-II |
|----------------------------|--|

Statistical analysis description:

Covariates in the MMRM were treatment group, EDSS strata (<4, >=4), geographic region (US, non-US), visit, treatment by visit interaction, baseline value, and baseline value-by-visit interaction.

| | |
|-------------------|--|
| Comparison groups | Teriflunomide 14 mg v Tolebrutinib 60 mg |
|-------------------|--|

| | |
|---|-----------------------------|
| Number of subjects included in analysis | 781 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[10] |
| P-value | = 0.0675 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | 1.873 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.135 |
| upper limit | 3.88 |

Notes:

[10] - A hierarchical testing procedure was used to control the overall type I error.

Secondary: Time to Onset of 6-Month Confirmed Disability Improvement (CDI) as Assessed by Expanded Disability Status Scale

| | |
|-----------------|---|
| End point title | Time to Onset of 6-Month Confirmed Disability Improvement (CDI) as Assessed by Expanded Disability Status Scale |
|-----------------|---|

End point description:

The EDSS was a disability scale that assessed the following 7 functional domains: visual, brainstem, pyramidal [motor], cerebellar [coordination], sensory, cerebral, and bowel/bladder. The total EDSS score ranged from 0 (normal) to 10 (death due to MS), increasing in increments of 0.5 points. Higher scores indicated increased disability. CDI was defined as a decrease of ≥ 1 point from baseline in the EDSS score lasting at least 6 months. The ITT population included all randomized participants according to the intervention group allocated by the randomization, irrespective of the study intervention received.

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

End point timeframe:

Baseline (Day 1) to approximately 48 months

| End point values | Teriflunomide 14 mg | Tolebrutinib 60 mg | | |
|-------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 488 | 486 | | |
| Units: months | | | | |
| median (full range (min-max)) | 12.04 (2.8 to 37.1) | 11.82 (2.8 to 33.0) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Time to Onset of 6-Month CDI as Assessed by EDSS |
|----------------------------|--|

Statistical analysis description:

Analysis was performed using Cox proportional-hazards model with robust variance estimation. Covariates were treatment group, Gd-enhancing T1 lesions at baseline (presence, absence), EDSS strata (<4 , ≥ 4), geographic region (US, non-US).

| | |
|-------------------|--|
| Comparison groups | Teriflunomide 14 mg v Tolebrutinib 60 mg |
|-------------------|--|

| | |
|---|-----------------------------|
| Number of subjects included in analysis | 974 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[11] |
| P-value | = 0.3594 ^[12] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.831 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.554 |
| upper limit | 1.245 |

Notes:

[11] - A hierarchical testing procedure was used to control the overall type I error.

[12] - Derived from log-rank test with stratification of EDSS strata (<4, >=4), geographic region (US, non-US).

Secondary: Percent Change in Brain Volume Loss at EOS Compared to Month 6

| | |
|-----------------|--|
| End point title | Percent Change in Brain Volume Loss at EOS Compared to Month 6 |
|-----------------|--|

End point description:

MRI of the brain was performed at the specified timepoints to detect the changes in brain volume loss. The ITT population included all randomized participants according to the intervention group allocated by the randomization, irrespective of the study intervention received. Only participants with data collected at specified timepoints are reported.

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

End point timeframe:

Month 6 to EOS (up to approximately 48 months)

| End point values | Teriflunomide 14 mg | Tolebrutinib 60 mg | | |
|-------------------------------------|---------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 346 | 351 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | -0.884 (± 0.0368) | -0.688 (± 0.0369) | | |

Statistical analyses

| | |
|----------------------------|-------------------------------------|
| Statistical analysis title | Percent Change in Brain Volume Loss |
|----------------------------|-------------------------------------|

Statistical analysis description:

Covariates in the MMRM were treatment group, EDSS strata (<4, >=4), geographic region (US, non-US), visit, treatment by visit interaction, cube root transformed Month 6 brain volume, and cube root transformed Month 6 brain volume-by-visit interaction.

| | |
|-------------------|--|
| Comparison groups | Teriflunomide 14 mg v Tolebrutinib 60 mg |
|-------------------|--|

| | |
|---|-----------------------------|
| Number of subjects included in analysis | 697 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[13] |
| P-value | = 0.0002 |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | 0.196 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.093 |
| upper limit | 0.298 |

Notes:

[13] - A hierarchical testing procedure was used to control the overall type I error.

Secondary: Change From Baseline in Multiple Sclerosis Quality of Life 54 (MSQoL-54) Questionnaire Score at EOS

| | |
|-----------------|---|
| End point title | Change From Baseline in Multiple Sclerosis Quality of Life 54 (MSQoL-54) Questionnaire Score at EOS |
|-----------------|---|

End point description:

MSQoL-54 consisted of 12 subscales & 2 single-item measures(satisfaction with sexual function[1 item]; change in health[1 item]).12 subscales were:a:physical health(10 items), b:health perceptions(5 items), c:energy(5 items), d:role limit physical(4 items), e:sexual function(4 items), f:pain(3 items), g:social function(3 items), h:health distress(4 items), i:overall quality of life(2 items), j:emotional well-being(5 items), k:role limitations emotional(3 items) and l:cognitive function(4 items).Physical & mental health composite score were calculated as weighted sum of 'a to h' & 'i to l' subscales respectively. Each composite score was transformed linearly to common 0(worst) to 100(best) score range;higher score indicated improved QoL. Baseline=last available value prior to first dose of study intervention.Analysis was performed on ITT population.Only participants with data collected at specified timepoints are reported. n=number of participants analyzed for each specified category.

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

End point timeframe:

Baseline (Day 1) to EOS (up to approximately 48 months)

| End point values | Teriflunomide 14 mg | Tolebrutinib 60 mg | | |
|--|------------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 400 | 399 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | | | | |
| Physical health composite score (n=393, 394) | -2.468 (± 0.7014) | -0.460 (± 0.7021) | | |
| Mental health composite score (n=400, 399) | -2.070 (± 0.8346) | -0.729 (± 0.8359) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-emergent Adverse Events

(TEAEs), Treatment-emergent Serious Adverse Events (TESAEs), TEAEs Leading to Permanent Study Intervention Discontinuation and Treatment-emergent Adverse Events of Special Interest (AESIs)

| | |
|-----------------|--|
| End point title | Number of Participants With Treatment-emergent Adverse Events (TEAEs), Treatment-emergent Serious Adverse Events (TESAEs), TEAEs Leading to Permanent Study Intervention Discontinuation and Treatment-emergent Adverse Events of Special Interest (AESIs) |
|-----------------|--|

End point description:

An AE was any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. SAE was any untoward medical occurrence that at any dose: resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent disability/incapacity, was a congenital anomaly/birth defect or was an important medical event. An AESI was an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program for which ongoing monitoring and immediate notification by the Investigator to the Sponsor was required. TEAEs were defined as AEs that developed, worsened or became serious during the TE period. Safety population included all randomized participants exposed to study intervention, regardless of amount of exposure, analyzed according to intervention actually received.

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

End point timeframe:

From first dose of study intervention (Day 1) up to the earliest of either 10 days post last dose, death or last contact; up to approximately 48 months

| End point values | Teriflunomide 14 mg | Tolebrutinib 60 mg | | |
|---|------------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 488 | 486 | | |
| Units: participants | | | | |
| TEAEs | 423 | 407 | | |
| TESAEs | 40 | 42 | | |
| TEAEs:permanent study intervention discontinuation | 24 | 23 | | |
| TEAESIs | 57 | 53 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (C_{max}) of Tolebrutinib and M2 Metabolite

| | |
|-----------------|---|
| End point title | Maximum Observed Plasma Concentration (C _{max}) of Tolebrutinib and M2 Metabolite ^[14] |
|-----------------|---|

End point description:

Blood samples were collected at specified timepoints to assess C_{max} of tolebrutinib and M2 metabolite using population pharmacokinetic (PK) model. The PK population included all participants in the safety population with at least 1 non-missing PK sample after first dose of the study intervention. Only participants with data collected at specified timepoints are reported.

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

End point timeframe:

30-90 minutes post-dose at Months 6, 9, and 12 and 2.5-5 hours post-dose at Months 6 and 12

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only participants in the Tolebrutinib 60 mg arm group were analyzed in this endpoint.

| | | | | |
|--------------------------------------|--------------------|--|--|--|
| End point values | Tolebrutinib 60 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 444 | | | |
| Units: nanogram/milliliter (ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Tolebrutinib | 12.0 (± 7.75) | | | |
| M2 Metabolite | 28.3 (± 15.8) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Observed Plasma Concentration (Tmax) of Tolebrutinib and M2 Metabolite

| | |
|-----------------|--|
| End point title | Time to Maximum Observed Plasma Concentration (Tmax) of Tolebrutinib and M2 Metabolite ^[15] |
|-----------------|--|

End point description:

Blood samples were collected at specified timepoints to assess Tmax of tolebrutinib and M2 metabolite using population PK model. The PK population included all participants in the safety population with at least 1 non-missing PK sample after first dose of the study intervention. Only participants with data collected at specified timepoints are reported.

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

End point timeframe:

30-90 minutes post-dose at Months 6, 9, and 12 and 2.5-5 hours post-dose at Months 6 and 12

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only participants in the Tolebrutinib 60 mg arm group were analyzed in this endpoint.

| | | | | |
|--------------------------------------|--------------------|--|--|--|
| End point values | Tolebrutinib 60 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 444 | | | |
| Units: hour (h) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Tolebrutinib | 1.28 (± 0.513) | | | |
| M2 Metabolite | 1.40 (± 0.508) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-time Curve Over the Last 24-hours Dosing Interval (AUC₀₋₂₄) of Tolebrutinib and M2 Metabolite

| | |
|-----------------|--|
| End point title | Area Under the Plasma Concentration-time Curve Over the Last 24-hours Dosing Interval (AUC ₀₋₂₄) of Tolebrutinib and M2 Metabolite ^[16] |
|-----------------|--|

End point description:

Blood samples were collected at specified timepoints to assess AUC₀₋₂₄ of tolebrutinib and M2 metabolite using population PK model. The PK population included all participants in the safety population with at least 1 non-missing PK sample after first dose of the study intervention. Only participants with data collected at specified timepoints are reported.

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

End point timeframe:

30-90 minutes post-dose at Months 6, 9, and 12 and 2.5-5 hours post-dose at Months 6 and 12

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only participants in the Tolebrutinib 60 mg arm group were analyzed in this endpoint.

| | | | | |
|--------------------------------------|--------------------|--|--|--|
| End point values | Tolebrutinib 60 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 444 | | | |
| Units: ng*h/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Tolebrutinib | 30.5 (± 18.2) | | | |
| M2 Metabolite | 76.7 (± 44.1) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Plasma Neurofilament Light Chain (NfL) and Serum Chitinase-3 Like Protein-1 (Chi3L1) Levels at EOS

| | |
|-----------------|--|
| End point title | Change From Baseline in Plasma Neurofilament Light Chain (NfL) and Serum Chitinase-3 Like Protein-1 (Chi3L1) Levels at EOS |
|-----------------|--|

End point description:

Blood samples were collected at specified timepoints to assess change from baseline in NfL and Chi3L1. Baseline was defined as the last available value prior to the first dose of study intervention. The safety population included all randomized participants exposed to the study intervention, regardless of the amount of exposure, analyzed according to the intervention actually received. Only participants with data collected at specified timepoints are reported. Here, n= number of participants analyzed for each specified category.

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

End point timeframe:

Baseline (Day 1) to EOS (up to approximately 48 months)

| End point values | Teriflunomide 14 mg | Tolebrutinib 60 mg | | |
|---------------------------------------|----------------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 344 | 350 | | |
| Units: picogram/mL | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| NfL (n=294, 296) | -1.665 (-6.100 to 0.830) | -0.325 (-3.505 to 2.220) | | |
| Chi3L1 (n=344, 350) | 1017.100 (-4494.850 to 7672.450) | 1572.250 (-2582.000 to 6356.600) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Cluster of Differentiation (CD)19+ B Cells at EOS

| | |
|-----------------|---|
| End point title | Change From Baseline in Cluster of Differentiation (CD)19+ B Cells at EOS |
|-----------------|---|

End point description:

Blood samples were collected at specified timepoints to assess change from baseline in CD19+ B cells. Baseline was defined as the last available value prior to the first dose of study intervention. The safety population included all randomized participants exposed to the study intervention, regardless of the amount of exposure, analyzed according to the intervention actually received. Only participants with data collected at specified timepoints are reported.

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

End point timeframe:

Baseline (Day 1) to EOS (up to approximately 48 months)

| End point values | Teriflunomide 14 mg | Tolebrutinib 60 mg | | |
|---------------------------------------|-----------------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 95 | 100 | | |
| Units: cells/microliter | | | | |
| median (inter-quartile range (Q1-Q3)) | -45.000 (-81.000 to -5.000) | -60.500 (-97.500 to -28.500) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Serum Immunoglobulin (Ig) Levels at EOS

| | |
|-----------------|---|
| End point title | Change From Baseline in Serum Immunoglobulin (Ig) Levels at EOS |
|-----------------|---|

End point description:

Blood samples were collected at specified timepoints to assess change from baseline in IgG and IgM

levels. Baseline was defined as the last available value prior to the first dose of study intervention. The safety population included all randomized participants exposed to the study intervention, regardless of the amount of exposure, analyzed according to the intervention actually received. Only participants with data collected at specified timepoints are reported. Here, n= number of participants analyzed for each specified category.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline (Day 1) to EOS (up to approximately 48 months) | |

| End point values | Teriflunomide 14 mg | Tolebrutinib 60 mg | | |
|---------------------------------------|------------------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 263 | 266 | | |
| Units: gram/liter | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| IgG (n=261, 266) | -0.660 (-1.460 to 0.150) | 0.235 (-0.500 to 1.020) | | |
| IgM (n=263, 263) | -0.150 (-0.330 to -0.030) | -0.340 (-0.520 to -0.190) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study intervention (Day 1) up to the earliest of either 10 days post last dose, death or last contact; up to approximately 48 months. Deaths were collected from baseline (Day 1) up to end of follow-up, approximately 48 months.

Adverse event reporting additional description:

Analysis was performed on the safety population. This was an event-driven (6-month CDW) trial with a variable treatment duration (EOS duration: up to approximately 48 months).

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 27.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------------|
| Reporting group title | Tolebrutinib 60 mg |
|-----------------------|--------------------|

Reporting group description:

Participants received tolebrutinib 60 mg tablet orally QD along with a placebo matched to teriflunomide orally QD up to approximately 48 months.

| | |
|-----------------------|---------------------|
| Reporting group title | Teriflunomide 14 mg |
|-----------------------|---------------------|

Reporting group description:

Participants received teriflunomide 14 mg tablet orally QD along with a placebo matched to tolebrutinib orally QD up to approximately 47 months.

| Serious adverse events | Tolebrutinib 60 mg | Teriflunomide 14 mg | |
|---|--------------------|---------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 42 / 486 (8.64%) | 40 / 488 (8.20%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Bladder Transitional Cell Carcinoma | | | |
| subjects affected / exposed | 0 / 486 (0.00%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Benign Ovarian Tumour | | | |
| subjects affected / exposed | 1 / 486 (0.21%) | 0 / 488 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Benign Bone Neoplasm | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 486 (0.21%) | 0 / 488 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Adenocarcinoma Of Colon | | | |
| subjects affected / exposed | 0 / 486 (0.00%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Breast Cancer Stage Ii | | | |
| subjects affected / exposed | 1 / 486 (0.21%) | 0 / 488 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Invasive Breast Carcinoma | | | |
| subjects affected / exposed | 1 / 486 (0.21%) | 0 / 488 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal Cancer | | | |
| subjects affected / exposed | 1 / 486 (0.21%) | 0 / 488 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Soft Tissue Sarcoma | | | |
| subjects affected / exposed | 0 / 486 (0.00%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine Leiomyoma | | | |
| subjects affected / exposed | 2 / 486 (0.41%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Varicose Vein | | | |
| subjects affected / exposed | 1 / 486 (0.21%) | 0 / 488 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive Crisis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 486 (0.00%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion Spontaneous | | | |
| subjects affected / exposed | 2 / 486 (0.41%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Uterine Haemorrhage | | | |
| subjects affected / exposed | 0 / 486 (0.00%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intermenstrual Bleeding | | | |
| subjects affected / exposed | 0 / 486 (0.00%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endometriosis | | | |
| subjects affected / exposed | 1 / 486 (0.21%) | 0 / 488 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Nasal Septum Deviation | | | |
| subjects affected / exposed | 0 / 486 (0.00%) | 2 / 488 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary Embolism | | | |
| subjects affected / exposed | 0 / 486 (0.00%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Thinking Abnormal | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 486 (0.00%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Transaminases Increased | | | |
| subjects affected / exposed | 1 / 486 (0.21%) | 0 / 488 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood Pressure Increased | | | |
| subjects affected / exposed | 0 / 486 (0.00%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Alanine Aminotransferase Increased | | | |
| subjects affected / exposed | 0 / 486 (0.00%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Meniscus Injury | | | |
| subjects affected / exposed | 1 / 486 (0.21%) | 0 / 488 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Limb Injury | | | |
| subjects affected / exposed | 0 / 486 (0.00%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint Dislocation | | | |
| subjects affected / exposed | 0 / 486 (0.00%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyphaema | | | |
| subjects affected / exposed | 1 / 486 (0.21%) | 0 / 488 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Forearm Fracture | | | |
| subjects affected / exposed | 1 / 486 (0.21%) | 0 / 488 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Burns Second Degree | | | |
| subjects affected / exposed | 1 / 486 (0.21%) | 0 / 488 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur Fracture | | | |
| subjects affected / exposed | 0 / 486 (0.00%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Patella Fracture | | | |
| subjects affected / exposed | 1 / 486 (0.21%) | 0 / 488 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple Fractures | | | |
| subjects affected / exposed | 1 / 486 (0.21%) | 0 / 488 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rib Fracture | | | |
| subjects affected / exposed | 1 / 486 (0.21%) | 0 / 488 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Supraventricular Tachycardia | | | |
| subjects affected / exposed | 0 / 486 (0.00%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Multiple Sclerosis Relapse | | | |
| subjects affected / exposed | 3 / 486 (0.62%) | 5 / 488 (1.02%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Epilepsy | | | |
| subjects affected / exposed | 1 / 486 (0.21%) | 0 / 488 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Central Nervous System Lesion | | | |
| subjects affected / exposed | 0 / 486 (0.00%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Optic Neuritis | | | |
| subjects affected / exposed | 0 / 486 (0.00%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sciatica | | | |
| subjects affected / exposed | 0 / 486 (0.00%) | 2 / 488 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Status Epilepticus | | | |
| subjects affected / exposed | 1 / 486 (0.21%) | 0 / 488 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Diplopia | | | |
| subjects affected / exposed | 0 / 486 (0.00%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Visual Impairment | | | |
| subjects affected / exposed | 1 / 486 (0.21%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Visual Field Defect | | | |
| subjects affected / exposed | 0 / 486 (0.00%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vision Blurred | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 486 (0.00%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Epulis | | | |
| subjects affected / exposed | 1 / 486 (0.21%) | 0 / 488 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal Ulcer Haemorrhage | | | |
| subjects affected / exposed | 1 / 486 (0.21%) | 0 / 488 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 486 (0.00%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal Pain Upper | | | |
| subjects affected / exposed | 1 / 486 (0.21%) | 0 / 488 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 486 (0.00%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis Acute | | | |
| subjects affected / exposed | 0 / 486 (0.00%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal Erosion | | | |
| subjects affected / exposed | 0 / 486 (0.00%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal Disorder | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 486 (0.00%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Food Poisoning | | | |
| subjects affected / exposed | 0 / 486 (0.00%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 486 (0.21%) | 0 / 488 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bile Duct Stone | | | |
| subjects affected / exposed | 0 / 486 (0.00%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug-Induced Liver Injury | | | |
| subjects affected / exposed | 1 / 486 (0.21%) | 0 / 488 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis Chronic | | | |
| subjects affected / exposed | 0 / 486 (0.00%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic Function Abnormal | | | |
| subjects affected / exposed | 0 / 486 (0.00%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Erythema Multiforme | | | |
| subjects affected / exposed | 1 / 486 (0.21%) | 0 / 488 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue | | | |

| | | | |
|---|-----------------|-----------------|--|
| disorders | | | |
| Intervertebral Disc Protrusion | | | |
| subjects affected / exposed | 0 / 486 (0.00%) | 2 / 488 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscular Weakness | | | |
| subjects affected / exposed | 1 / 486 (0.21%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteonecrosis | | | |
| subjects affected / exposed | 1 / 486 (0.21%) | 0 / 488 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain In Extremity | | | |
| subjects affected / exposed | 0 / 486 (0.00%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rotator Cuff Syndrome | | | |
| subjects affected / exposed | 0 / 486 (0.00%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 2 / 486 (0.41%) | 0 / 488 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Covid-19 | | | |
| subjects affected / exposed | 1 / 486 (0.21%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Covid-19 Pneumonia | | | |
| subjects affected / exposed | 4 / 486 (0.82%) | 2 / 488 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Chronic Sinusitis | | | |
| subjects affected / exposed | 0 / 486 (0.00%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic Tonsillitis | | | |
| subjects affected / exposed | 1 / 486 (0.21%) | 0 / 488 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory Tract Chlamydial Infection | | | |
| subjects affected / exposed | 0 / 486 (0.00%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis Acute | | | |
| subjects affected / exposed | 1 / 486 (0.21%) | 0 / 488 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 486 (0.21%) | 0 / 488 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 0 / 486 (0.00%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral Upper Respiratory Tract Infection | | | |
| subjects affected / exposed | 0 / 486 (0.00%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cystitis | | | |
| subjects affected / exposed | 0 / 486 (0.00%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Salpingo-Oophoritis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 486 (0.21%) | 0 / 488 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Systemic Viral Infection | | | |
| subjects affected / exposed | 0 / 486 (0.00%) | 1 / 488 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enteritis Infectious | | | |
| subjects affected / exposed | 1 / 486 (0.21%) | 0 / 488 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Tolebrutinib 60 mg | Teriflunomide 14 mg | |
|---|---------------------------|----------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 296 / 486 (60.91%) | 321 / 488 (65.78%) | |
| Investigations | | | |
| Alanine Aminotransferase Increased | | | |
| subjects affected / exposed | 23 / 486 (4.73%) | 40 / 488 (8.20%) | |
| occurrences (all) | 26 | 43 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 16 / 486 (3.29%) | 27 / 488 (5.53%) | |
| occurrences (all) | 19 | 28 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 56 / 486 (11.52%) | 44 / 488 (9.02%) | |
| occurrences (all) | 100 | 62 | |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 14 / 486 (2.88%) | 58 / 488 (11.89%) | |
| occurrences (all) | 22 | 93 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |

| | | | |
|--|--|---|--|
| subjects affected / exposed occurrences (all) | 22 / 486 (4.53%) 24 | 36 / 488 (7.38%) 50 | |
| Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) | 36 / 486 (7.41%) 36 | 73 / 488 (14.96%) 75 | |
| Psychiatric disorders Depression subjects affected / exposed occurrences (all) | 11 / 486 (2.26%) 11 | 27 / 488 (5.53%) 27 | |
| Musculoskeletal and connective tissue disorders Back Pain subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) | 31 / 486 (6.38%) 35 18 / 486 (3.70%) 25 | 30 / 488 (6.15%) 34 27 / 488 (5.53%) 31 | |
| Infections and infestations Covid-19 subjects affected / exposed occurrences (all) Viral Upper Respiratory Tract Infection subjects affected / exposed occurrences (all) Urinary Tract Infection subjects affected / exposed occurrences (all) Upper Respiratory Tract Infection subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) | 117 / 486 (24.07%) 133 31 / 486 (6.38%) 54 34 / 486 (7.00%) 45 46 / 486 (9.47%) 69 59 / 486 (12.14%) 88 19 / 486 (3.91%) 24 | 135 / 488 (27.66%) 150 34 / 488 (6.97%) 48 27 / 488 (5.53%) 32 46 / 488 (9.43%) 65 41 / 488 (8.40%) 61 26 / 488 (5.33%) 35 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 07 May 2020 | The purpose of the amendment was to add exclusion criteria that were previously omitted and to meet the regulatory requirement of a benefit/risk evaluation of the study in the context of the Coronavirus Disease 2019 pandemic. |
| 24 August 2020 | The purpose of the amendment was to respond to European Health Authorities' requests. |
| 28 September 2020 | The purpose of the amendment was to respond to Japanese Health Authorities' requests. |
| 14 April 2021 | The purpose of the amendment was to update the liver function test frequency in the European Union countries in accordance with the updated teriflunomide (Aubagio) summary of product characteristics. Alanine aminotransferase (ALT) exclusion criterion was also updated to align with the Aubagio label. |
| 18 November 2021 | The purpose of the amendment was to update the safety follow-up algorithms for ALT increase and thrombocytopenia and the platelet level threshold for definition of an AESI in order to harmonize them with the other studies in the Phase 3 program. |
| 24 May 2022 | The purpose of the amendment was to update liver related exclusion criteria and monitoring to mitigate risk of drug-induced liver injury (DILI). |
| 13 September 2022 | The purpose of the amendment was to further reduce the risk of DILI by increasing the intensity of liver monitoring. |
| 12 December 2022 | The purpose of the amendment was to clarify information about DILI and update the ALT increase algorithm in relation to the risk of DILI. |
| 17 November 2023 | The purpose of the amendment was to update the testing requirements in the "Increase in ALT algorithm" and update the country-specific requirements for Japan with additional guidelines in case of ALT increase >3 x upper limit of normal as per Health Authorities requests. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported