Clinical trial results:
A randomized, double-blind, double-dummy, parallel-group study comparing the efficacy and safety of ofatumumab versus teriflunomide in patients with relapsing multiple sclerosis

Summary

EudraCT number	2015-005419-33
Trial protocol	DE HU BE FI GB AT CZ PT SK ES LV LT BG FR HR IT
Global end of trial date	22 October 2020

Results information

Result version number	v1 (current)
This version publication date	06 November 2021
First version publication date	06 November 2021

Trial information

Trial identification

Sponsor protocol code	COMB157G2302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02792231
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.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	22 October 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 October 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Demonstrate that ofatumumab 20 mg s.c. once every 4 weeks is superior to teriflunomide 14 mg p.o. once daily in reducing the frequency of confirmed relapses as evaluated by the annualized relapse rate (ARR) in patients with relapsing multiple sclerosis (RMS).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 August 2016
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	Argentina: 8
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Austria: 20
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Bulgaria: 24
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	Croatia: 61
Country: Number of subjects enrolled	Czechia: 42
Country: Number of subjects enrolled	Finland: 3
Country: Number of subjects enrolled	France: 19
Country: Number of subjects enrolled	Germany: 43
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	India: 31
Country: Number of subjects enrolled	Italy: 26
Country: Number of subjects enrolled	Latvia: 15
Country: Number of subjects enrolled	Lithuania: 21
Country: Number of subjects enrolled	Mexico: 3
Country: Number of subjects enrolled	Norway: 2
Country: Number of subjects enrolled	Peru: 8

Country: Number of subjects enrolled	Poland: 46
Country: Number of subjects enrolled	Portugal: 36
Country: Number of subjects enrolled	Russian Federation: 199
Country: Number of subjects enrolled	Slovakia: 7
Country: Number of subjects enrolled	South Africa: 11
Country: Number of subjects enrolled	Spain: 52
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	Taiwan: 2
Country: Number of subjects enrolled	Turkey: 10
Country: Number of subjects enrolled	United Kingdom: 30
Country: Number of subjects enrolled	United States: 200
Worldwide total number of subjects	955
EEA total number of subjects	435

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)	955
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

It was pre-specified in the protocol to combine the data from this study with study NCT02792218 (COMB157G2301) for some outcome measures. Please refer to NCT02792218 for Participant Flow and Baseline Characteristics for participants from other study.

Pre-assignment

Screening details:

A total of 1280 patients were screened, of whom 955 patients were randomized into the study.

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, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	OMB 20 mg

Arm description:

Ofatumumab 20 mg s.c. injections on Days 1, 7, 14, Week 4 and every 4 weeks thereafter (+ teriflunomide-matching placebo capsule orally once daily)

Arm type	Experimental
Investigational medicinal product name	Placebo matching teriflunomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Teriflunomide-matching placebo capsule orally once daily

Investigational medicinal product name	Ofatumumab
Investigational medicinal product code	OMB157
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Ofatumumab 20 mg pre-filled syringes for subcutaneous injection on Days 1 ,7,14, Week 4 and every 4 weeks thereafter

Arm title	TER 14 mg

Arm description:

Teriflunomide 14 mg capsule orally once daily (+ ofatumumab-matching placebo injections on Days 1, 7, 14, Week 4 and every 4 weeks thereafter)

Arm type	Active comparator
Investigational medicinal product name	Teriflunomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Teriflunomide 14 mg capsule orally once daily

Investigational medicinal product name	Placebo matching ofatumumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Ofatumumab-matching placebo subcutaneous injections on Days 1, 7, 14, Week 4 and every 4 weeks thereafter

Number of subjects in period 1	OMB 20 mg	TER 14 mg
Started	481	474
Completed	399	390
Not completed	82	84
Physician decision	14	12
Adverse event, non-fatal	15	11
Technical problems	-	1
Non-compliance with study treatment	2	1
Protocol deviation	2	-
Pregnancy	1	3
Patient/guardian decision	32	42
Lost to follow-up	9	5
Lack of efficacy	7	9

Baseline characteristics

Reporting groups	
Reporting group title	OMB 20 mg
Reporting group description:	
Ofatumumab 20 mg s.c. injections on Days 1, 7, 14, Week 4 and every 4 weeks thereafter (+ teriflunomide-matching placebo capsule orally once daily)	
Reporting group title	TER 14 mg
Reporting group description:	
Teriflunomide 14 mg capsule orally once daily (+ ofatumumab-matching placebo injections on Days 1, 7, 14, Week 4 and every 4 weeks thereafter)	

Reporting group values	OMB 20 mg	TER 14 mg	Total
Number of subjects	481	474	955
Age categorical Units: Subjects			
Adults (18-64 years)	481	474	955
Age Continuous Units: Years			
arithmetic mean	38.0	38.2	
standard deviation	± 9.28	± 9.47	-
Sex: Female, Male Units: Participants			
Female	319	319	638
Male	162	155	317
Race/Ethnicity, Customized Units: Subjects			
Asian	21	19	40
Black or African American	13	18	31
White	418	417	835
Other	20	14	34
Unknown	9	6	15
Number of relapses in the past 12 months prior to screening			
Reported numbers are from investigator records			
Units: Number of relapses			
arithmetic mean	1.3	1.3	
standard deviation	± 0.74	± 0.73	-
Expanded Disability Status Scale (EDSS)			
The EDSS uses an ordinal scale to assess neurologic impairment in MS based on a neurological examination. Scores in each of 7 functional systems (Visual, Brain Stem, Pyramidal, Cerebellar,Sensory, Bowel & Bladder, and Cerebral) and an ambulation score were combined to determine the EDSS steps, ranging from 0 (normal) to 10 (death due to MS).			
Units: Score on a scale			
arithmetic mean	2.90	2.86	
standard deviation	± 1.343	± 1.373	-
Number of Gd-enhancing T1 lesions			
Magnetic Resonance Imaging (MRI) scans of the brain were were read by the central MRI reading center. The central reading center was blinded with no access to information on treatment assignments			
Units: T1 lesions			
arithmetic mean	1.6	1.5	

standard deviation	± 4.07	± 4.07	-

End points

End points reporting groups

Reporting group title	OMB 20 mg
Reporting group description:	
Ofatumumab 20 mg s.c. injections on Days 1, 7, 14, Week 4 and every 4 weeks thereafter (+ teriflunomide-matching placebo capsule orally once daily)	
Reporting group title	TER 14 mg
Reporting group description:	
Teriflunomide 14 mg capsule orally once daily (+ ofatumumab-matching placebo injections on Days 1, 7, 14, Week 4 and every 4 weeks thereafter)	
Subject analysis set title	OMB 20 mg - Pooled
Subject analysis set type	Full analysis
Subject analysis set description:	
Ofatumumab 20 mg s.c. injections on Days 1, 7, 14, Week 4 and every 4 weeks thereafter (+ teriflunomide-matching placebo capsule orally once daily). Full analysis set from combined studies.	
Subject analysis set title	TER 14 mg - Pooled
Subject analysis set type	Full analysis
Subject analysis set description:	
Teriflunomide 14 mg capsule orally once daily (+ ofatumumab-matching placebo injections on Days 1, 7, 14, Week 4 and every 4 weeks thereafter). Full analysis set from combined studies.	

Primary: Annualized relapse rate (ARR)

End point title	Annualized relapse rate (ARR)
End point description:	
ARR was the number of confirmed relapses in a year, calculated as the total number of relapses for all participants in the treatment group divided by the total participant-years of time in study. A confirmed MS relapse was defined as one accompanied by a clinically-relevant change in the EDSS performed by the Independent EDSS rater, i.e. an increase of at least 0.5 points on the EDSS score, or an increase of 1 point on two functional scores or 2 points on one functional score (excluding changes involving bowel/bladder or cerebral functional system). Comparisons were made to the previous rating (the last EDSS rating that did not occur during a relapse).	
End point type	Primary
End point timeframe:	
Baseline up to 2.5 years	

End point values	OMB 20 mg	TER 14 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	469	470		
Units: number of relapses in a year				
arithmetic mean (confidence interval 95%)	0.10 (0.08 to 0.13)	0.25 (0.21 to 0.30)		

Statistical analyses

Statistical analysis title	ARR
Statistical analysis description:	
Obtained from fitting a negative binomial regression model with log-link to the number of relapses,	

adjusted for treatment and region as factors, number of relapses in previous year, baseline EDSS, baseline number of Gd-enhancing lesions and the patient's age at baseline as covariates. The natural log of the time-in-study was used as offset to annualize the relapse rate.

Comparison groups	OMB 20 mg v TER 14 mg
Number of subjects included in analysis	939
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	negative binomial regression model
Parameter estimate	rate ratio
Point estimate	0.416
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.309
upper limit	0.56

Secondary: 3-month confirmed disability worsening (3mCDW) based on EDSS - Pooled Data

End point title	3-month confirmed disability worsening (3mCDW) based on EDSS - Pooled Data

End point description:

A 3-month confirmed disability worsening (3mCDW) was defined as an increase from baseline in Expanded Disability Status Scale (EDSS) score sustained for at least 3 months. For patients with a baseline EDSS of 0, the criterion for disability worsening was an increase in EDSS of ≥1.5, for patients with a baseline EDSS of 1 to 5 or ≥5.5, the criterion for disability worsening was an increase in EDSS of ≥1 or ≥0.5, respectively. This study was not powered for the analysis of this endpoint individually. It was pre-specified in the study protocol to combine the data from this study with study COMB157G2301 to address this endpoint.

End point type	Secondary

End point timeframe:

Baseline, every 3 months up to 2.5 years

End point values	OMB 20 mg - Pooled	TER 14 mg - Pooled		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	944	932		
Units: percentage of participants				
number (confidence interval 95%)				
Month 18 - from Kaplan Meier estimates	9.4 (7.6 to 11.5)	13.5 (11.4 to 16.0)		
Month 24 - from Kaplan Meier estimates	10.9 (8.8 to 13.4)	15.0 (12.6 to 17.7)		

Statistical analyses

Statistical analysis title	3mCDW - pooled

Statistical analysis description:

Pooled data - this study was not powered for the analysis of this endpoint individually. It was pre-specified in the study protocol to combine the data from this study with study COMB157G2301 to address this endpoint.

Comparison groups	OMB 20 mg - Pooled v TER 14 mg - Pooled
Number of subjects included in analysis	1876
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.003
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.657
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	0.863

Secondary: 3-month confirmed disability worsening (3mCDW) based on EDSS - Study COMB157G2302

End point title	3-month confirmed disability worsening (3mCDW) based on EDSS - Study COMB157G2302

End point description:

A 3-month confirmed disability worsening (3mCDW) was defined as an increase from baseline in Expanded Disability Status Scale (EDSS) score sustained for at least 3 months. For patients with a baseline EDSS of 0, the criterion for disability worsening was an increase in EDSS of ≥1.5, for patients with a baseline EDSS of 1 to 5 or ≥5.5, the criterion for disability worsening was an increase in EDSS of ≥1 or ≥0.5, respectively. This study was not powered for the analysis of this endpoint individually. It was pre-specified in the study protocol to combine the data from this study with study COMB157G2301 to address this endpoint.

End point type	Secondary

End point timeframe:

Baseline, every 3 months up to 2.5 years

End point values	OMB 20 mg	TER 14 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	479	473		
Units: percentage of participants				
number (confidence interval 95%)				
Month 18 - from Kaplan Meier estimates	9.3 (6.9 to 12.5)	13.2 (10.3 to 16.7)		
Month 24 - from Kaplan Meier estimates	10.5 (7.8 to 14.1)	14.6 (11.5 to 18.6)		

Statistical analyses

Statistical analysis title	3mCDW - pooled

Statistical analysis description:

This study was not powered for the analysis of this endpoint individually. It was pre-specified in the study protocol to combine the data from this study with study COMB157G2301 to address this endpoint.

Comparison groups	OMB 20 mg v TER 14 mg
Number of subjects included in analysis	952
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.038
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.662
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.449
upper limit	0.977

Secondary: 6-month confirmed disability worsening (6mCDW) based on EDSS - Pooled Data

End point title	6-month confirmed disability worsening (6mCDW) based on EDSS - Pooled Data

End point description:

A 6-month confirmed disability worsening (6mCDW) was defined as an increase from baseline in Expanded Disability Status Scale (EDSS) score sustained for at least 6 months. For patients with a baseline EDSS of 0, the criterion for disability worsening was an increase in EDSS of ≥1.5, for patients with a baseline EDSS of 1 to 5 or ≥5.5, the criterion for disability worsening was an increase in EDSS of ≥1 or ≥0.5, respectively. This study was not powered for the analysis of this endpoint individually. It was pre-specified in the study protocol to combine the data from this study with study COMB157G2301 to address this endpoint.

End point type	Secondary

End point timeframe:

Baseline, every 3 months up to 2.5 years

End point values	OMB 20 mg - Pooled	TER 14 mg - Pooled		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	944	932		
Units: percentage of participants				
number (confidence interval 95%)				
Month 18- from Kaplan Meier estimates	7.8 (6.2 to 9.7)	10.7 (8.9 to 13.0)		
Month 24 - from Kaplan Meier estimates	8.1 (6.5 to 10.2)	12.0 (9.9 to 14.5)		

Statistical analyses

Statistical analysis title	6mCDW - pooled

Statistical analysis description:

This study was not powered for the analysis of this endpoint individually. It was pre-specified in the study protocol to combine the data from this study with study COMB157G2301 to address this endpoint.

Comparison groups	OMB 20 mg - Pooled v TER 14 mg - Pooled
Number of subjects included in analysis	1876
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.012
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.676
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.498
upper limit	0.917

Secondary: 6-month confirmed disability worsening (6mCDW) based on EDSS - Study COMB157G2302

End point title	6-month confirmed disability worsening (6mCDW) based on EDSS - Study COMB157G2302

End point description:

A 6-month confirmed disability worsening (6mCDW) was defined as an increase from baseline in Expanded Disability Status Scale (EDSS) score sustained for at least 6 months. For patients with a baseline EDSS of 0, the criterion for disability worsening was an increase in EDSS of ≥1.5, for patients with a baseline EDSS of 1 to 5 or ≥5.5, the criterion for disability worsening was an increase in EDSS of ≥1 or ≥0.5, respectively. This study was not powered for the analysis of this endpoint individually. It was pre-specified in the study protocol to combine the data from this study with study COMB157G2301 to address this endpoint.

End point type	Secondary

End point timeframe:

Baseline, every 3 months up to 2.5 years

End point values	OMB 20 mg	TER 14 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	479	473		
Units: percentage of participants				
number (confidence interval 95%)				
Month 18- from Kaplan Meier estimates	8.0 (5.9 to 11.0)	10.0 (7.5 to 13.2)		
Month 24 - from Kaplan Meier estimates	8.0 (5.9 to 11.0)	10.9 (8.2 to 14.4)		

Statistical analyses

Statistical analysis title	6mCDW - pooled

Statistical analysis description:

This study was not powered for the analysis of this endpoint individually. It was pre-specified in the study protocol to combine the data from this study with study COMB157G2301 to address this endpoint.

Comparison groups	OMB 20 mg v TER 14 mg
Number of subjects included in analysis	952
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.215
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.759
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	1.174

Secondary: 6-month confirmed disability improvement (6mCDI) based on EDSS - Pooled Data

End point title	6-month confirmed disability improvement (6mCDI) based on EDSS - Pooled Data

End point description:

A 6-month confirmed disability improvement (6mCDI) was defined as a decrease from baseline EDSS sustained for at least 6 months. For patients with a baseline EDSS of 0 to 1.5, no disability improvement was possible based on the protocol definition of an improvement; for patients with a baseline EDSS of ≥2 to 6 or ≥6.5 to 9.5, the criterion for disability improvement was a decrease in EDSS of ≤1 or ≤0.5, respectively. This study was not powered for the analysis of this endpoint individually. It was pre-specified in the study protocol to combine the data from this study with study COMB157G2301 to address this endpoint.

End point type	Secondary

End point timeframe:

Baseline, every 3 months up to 2.5 years

End point values	OMB 20 mg - Pooled	TER 14 mg - Pooled		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	749	724		
Units: percentage of participants				
number (confidence interval 95%)				
Month 18 - from Kaplan Meier estimates	10.1 (8.1 to 12.6)	7.6 (5.8 to 9.8)		
Month 24 - from Kaplan Meier estimates	11.0 (8.8 to 13.7)	8.2 (6.3 to 10.6)		

Statistical analyses

Statistical analysis title	6mCDI - pooled

Statistical analysis description:

This study was not powered for the analysis of this endpoint individually. It was pre-specified in the study protocol to combine the data from this study with study COMB157G2301 to address this endpoint.

Comparison groups	OMB 20 mg - Pooled v TER 14 mg - Pooled
Number of subjects included in analysis	1473
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.092
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.355
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.952
upper limit	1.928

Secondary: 6-month confirmed disability improvement (6mCDI) based on EDSS - Study COMB157G2302

End point title	6-month confirmed disability improvement (6mCDI) based on EDSS - Study COMB157G2302

End point description:

A 6-month confirmed disability improvement (6mCDI) was defined as a decrease from baseline EDSS sustained for at least 6 months. For patients with a baseline EDSS of 0 to 1.5, no disability improvement was possible based on the protocol definition of an improvement; for patients with a baseline EDSS of ≥2 to 6 or ≥6.5 to 9.5, the criterion for disability improvement was a decrease in EDSS of ≤1 or ≤0.5, respectively. This study was not powered for the analysis of this endpoint individually. It was pre-specified in the study protocol to combine the data from this study with study COMB157G2301 to address this endpoint.

End point type	Secondary

End point timeframe:

Baseline, every 3 months up to 2.5 years

End point values	OMB 20 mg	TER 14 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	374	361		
Units: percentage of participants				
number (confidence interval 95%)				
Month 18 - from Kaplan Meier estimates	11.1 (8.2 to 14.8)	8.1 (5.6 to 11.6)		
Month 24 - from Kaplan Meier estimates	12.3 (9.1 to 16.5)	8.1 (5.6 to 11.6)		

Statistical analyses

Statistical analysis title	6mCDI

Statistical analysis description:

This study was not powered for the analysis of this endpoint individually. It was pre-specified in the study protocol to combine the data from this study with study COMB157G2301 to address this endpoint.

Comparison groups	OMB 20 mg v TER 14 mg
Number of subjects included in analysis	735
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.09
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.523
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.936
upper limit	2.477

Secondary: Number of gadolinium-enhancing T1 lesions per MRI scan

End point title	Number of gadolinium-enhancing T1 lesions per MRI scan

End point description:

Total number of Gd-enhancing T1 lesions across all scans per patient adjusted for different number of scans due to variable follow-up time in study.

End point type	Secondary

End point timeframe:

Baseline, yearly up to 2.5 years

End point values	OMB 20 mg	TER 14 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	438	433		
Units: lesions per scan				
arithmetic mean (confidence interval 95%)	0.0317 (0.021 to 0.048)	0.5172 (0.404 to 0.662)		

Statistical analyses

Statistical analysis title	Gd + T1 Lesions
Comparison groups	OMB 20 mg v TER 14 mg

Number of subjects included in analysis	871
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	negative binomial regression model
Parameter estimate	rate ratio
Point estimate	0.061
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.037
upper limit	0.101

Secondary: Number of new or enlarging T2 lesions on MRI per year (annualized lesion rate)

End point title	Number of new or enlarging T2 lesions on MRI per year (annualized lesion rate)

End point description:

Number of new/enlarging T2 lesions on last available MRI scan compared to baseline adjusted for different time of scans versus baseline due to variable follow up time in study

End point type	Secondary

End point timeframe:

Baseline, yearly up to 2.5 years

End point values	OMB 20 mg	TER 14 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	448	442		
Units: T2 lesions per year				
arithmetic mean (confidence interval 95%)				
Month 12 n=422,410	0.94 (0.80 to 1.11)	4.41 (3.83 to 5.08)		
Month 24 n=90,76	0.72 (0.51 to 1.02)	3.72 (2.68 to 5.18)		
EOS n=448,442	0.64 (0.55 to 0.75)	4.16 (3.64 to 4.75)		

Statistical analyses

Statistical analysis title	T2 Lesions Month 12

Statistical analysis description:

Month 12

Comparison groups	OMB 20 mg v TER 14 mg

Number of subjects included in analysis	890
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	negative binomial regression model
Parameter estimate	rate ratio
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	0.27

Statistical analysis title	T2 Lesions End of Study
Statistical analysis description: End of Study	
Comparison groups	OMB 20 mg v TER 14 mg
Number of subjects included in analysis	890
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	negative binomial regression model
Parameter estimate	rate ratio
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.13
upper limit	0.19

Statistical analysis title	T2 Lesions Month 24
Statistical analysis description: Month 24	
Comparison groups	OMB 20 mg v TER 14 mg
Number of subjects included in analysis	890
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	negative binomial regression model
Parameter estimate	rate ratio
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	0.31

Secondary: Neurofilament light chain (NfL) concentration in serum

End point title	Neurofilament light chain (NfL) concentration in serum
End point description:	
The NfL concentration (geometric mean concentration) was estimated by treatment and time point with using a repeated measures model on the basis of all evaluable log-transformed NfL values.	
End point type	Secondary
End point timeframe:	
Month 3, 12 and 24	

End point values	OMB 20 mg	TER 14 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	425	423		
Units: pg/mL				
geometric mean (confidence interval 95%)				
Month 3 n=425,423	8.92 (8.62 to 9.23)	10.02 (9.68 to 10.36)		
Month 12 n=406,406	7.06 (6.77 to 7.37)	9.53 (9.13 to 9.95)		
Month 24 n=345,349	6.80 (6.47 to 7.13)	8.99 (8.57 to 9.44)		

Statistical analyses

Statistical analysis title	NfL Month 3
Statistical analysis description:	
Month 3	
Comparison groups	OMB 20 mg v TER 14 mg
Number of subjects included in analysis	848
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Geo-mean ratio
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	0.93

Statistical analysis title	NfL Month 12
Statistical analysis description: Month 12	
Comparison groups	OMB 20 mg v TER 14 mg
Number of subjects included in analysis	848
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Geo-mean ratio
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	0.79

Statistical analysis title	NfL Month 24
Statistical analysis description: Month 24	
Comparison groups	OMB 20 mg v TER 14 mg
Number of subjects included in analysis	848
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Geo-mean ratio
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	0.81

Secondary: Annualized rate of brain volume loss based on assessments of percent brain volume change from baseline

End point title	Annualized rate of brain volume loss based on assessments of percent brain volume change from baseline
End point description: Percent change from baseline in brain volume loss (BVL) on all MRI scans adjusted for different time of scan versus baseline due to variable follow up time in study	
End point type	Secondary
End point timeframe: Baseline, Months 12 and 24	

End point values	OMB 20 mg	TER 14 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	437	433		
Units: percentage of brain volume loss				
arithmetic mean (confidence interval 95%)	-0.29 (-0.35 to -0.23)	-0.35 (-0.42 to -0.29)		

Statistical analyses

Statistical analysis title	Brain volume loss
Comparison groups	OMB 20 mg v TER 14 mg
Number of subjects included in analysis	870
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.128
Method	random coefficient model
Parameter estimate	Mean difference (net)
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.15

Secondary: Participants with confirmed relapse

End point title	Participants with confirmed relapse

End point description:

A confirmed MS relapse was defined as one accompanied by a clinically-relevant change in the EDSS performed by the Independent EDSS rater, i.e. an increase of at least 0.5 points on the EDSS score, or an increase of 1 point on two functional scores or 2 points on one functional score (excluding changes involving bowel/bladder or cerebral functional system).

End point type	Secondary

End point timeframe:

Baseline up to 2.5 years

End point values	OMB 20 mg	TER 14 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	469	470		
Units: percentage of participants				
number (confidence interval 95%)	16.51 (13.18 to 20.57)	32.68 (28.10 to 37.79)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized relapse rate (ARR) >8 weeks after onset of treatment

End point title	Annualized relapse rate (ARR) >8 weeks after onset of treatment

End point description:

ARR was the number of confirmed relapses in a year, calculated as the total number of relapses for all participants in the treatment group divided by the total participant-years of time in study. A confirmed MS relapse was defined as one accompanied by a clinically-relevant change in the EDSS performed by the Independent EDSS rater, i.e. an increase of at least 0.5 points on the EDSS score, or an increase of 1 point on two functional scores or 2 points on one functional score (excluding changes involving bowel/bladder or cerebral functional system). Comparisons were made to the previous rating (the last EDSS rating that did not occur during a relapse).

End point type	Secondary

End point timeframe:

Baseline up to 2.5 years

End point values	OMB 20 mg	TER 14 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	461	467		
Units: number of relapses in a year				
arithmetic mean (confidence interval 95%)	0.096 (0.05 to 0.14)	0.241 (0.16 to 0.32)		

Statistical analyses

No statistical analyses for this end point

Secondary: 3-month confirmed disability worsening (3mCDW) based on EDSS > 8 weeks after onset of treatment - Pooled Data

End point title	3-month confirmed disability worsening (3mCDW) based on EDSS > 8 weeks after onset of treatment - Pooled Data

End point description:

A 3-month confirmed disability worsening (3mCDW) was defined as an increase from baseline in Expanded Disability Status Scale (EDSS) score sustained for at least 3 months. For patients with a baseline EDSS of 0, the criterion for disability worsening was an increase in EDSS of ≥1.5, for patients with a baseline EDSS of 1 to 5 or ≥5.5, the criterion for disability worsening was an increase in EDSS of ≥1 or ≥0.5, respectively. This study was not powered for the analysis of this endpoint individually. It was pre-specified in the study protocol to combine the data from this study with study COMB157G2301

to address this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to 2.5 years

End point values	OMB 20 mg - Pooled	TER 14 mg - Pooled		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	944	932		
Units: percentage of participants				
number (confidence interval 95%)				
Month 18 - from Kaplan Meier estimates	9.4 (7.6 to 11.5)	13.5 (11.4 to 16.0)		
Month 24 - from Kaplan Meier estimates	10.9 (8.8 to 13.4)	15.0 (12.6 to 17.7)		

Statistical analyses

Statistical analysis title	3mCDW >8 weeks

Statistical analysis description:

This study was not powered for the analysis of this endpoint individually. It was pre-specified in the study protocol to combine the data from this study with study COMB157G2301 to address this endpoint.

Comparison groups	OMB 20 mg - Pooled v TER 14 mg - Pooled
Number of subjects included in analysis	1876
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.002
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.641
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.486
upper limit	0.847

Secondary: 6-month confirmed disability worsening (6mCDW) based on EDSS > 8 weeks after onset of treatment - Pooled Data

End point title	6-month confirmed disability worsening (6mCDW) based on EDSS > 8 weeks after onset of treatment - Pooled Data

End point description:

A 6-month confirmed disability worsening (6mCDW) was defined as an increase from baseline in Expanded Disability Status Scale (EDSS) score sustained for at least 6 months. For patients with a baseline EDSS of 0, the criterion for disability worsening was an increase in EDSS of ≥1.5, for patients with a baseline EDSS of 1 to 5 or ≥5.5, the criterion for disability worsening was an increase in EDSS of ≥1 or ≥0.5, respectively. This study was not powered for the analysis of this endpoint individually. It was pre-specified in the study protocol to combine the data from this study with study COMB157G2301

to address this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to 2.5 years

End point values	OMB 20 mg - Pooled	TER 14 mg - Pooled		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	944	932		
Units: percentage of participants				
number (confidence interval 95%)				
Month 18- from Kaplan Meier estimates	7.8 (6.2 to 9.7)	10.7 (8.9 to 13.0)		
Month 24 - from Kaplan Meier estimates	8.1 (6.5 to 10.2)	12.0 (9.9 to 14.5)		

Statistical analyses

Statistical analysis title	6mCDW>8 weeks

Statistical analysis description:

This study was not powered for the analysis of this endpoint individually. It was pre-specified in the study protocol to combine the data from this study with study COMB157G2301 to address this endpoint.

Comparison groups	OMB 20 mg - Pooled v TER 14 mg - Pooled
Number of subjects included in analysis	1876
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.008
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.657
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.481
upper limit	0.898

Secondary: 6-month confirmed cognitive decline on Symbol Digit Modalities Test (SDMT) - Pooled Data

End point title	6-month confirmed cognitive decline on Symbol Digit Modalities Test (SDMT) - Pooled Data

End point description:

A 6-month confirmed cognitive decline was defined as a decrease from baseline of at least 4 points in SDMT score sustained for at least 6 months. Processing speed was measured by the Symbol Digit Modalities Test (SDMT) score. SDMT measures the time to pair abstract symbols with specific numbers. The test requires visuoperceptual processing, working memory, and psychomotor speed. The score is the number of correctly coded items in 90 seconds. (max=110, min=0). Higher scores indicate improvement. Lower scores indicate worsening. This study was not powered for the analysis of this

endpoint individually. It was pre-specified in the study protocol to combine the data from this study with study COMB157G2301 to address this endpoint

End point type	Secondary

End point timeframe:

Baseline, every 6 months up to 2.5 years

End point values	OMB 20 mg - Pooled	TER 14 mg - Pooled		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	930	917		
Units: percentage of participants				
number (confidence interval 95%)				
Month 18 - from Kaplan Meier estimates	14.3 (12.2 to 16.8)	13.7 (11.5 to 16.1)		
Month 24 - from Kaplan Meier estimates	15.4 (13.1 to 18.2)	14.0 (11.8 to 16.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: 6-month confirmed disability worsening (6mCDW) or 6-month confirmed cognitive decline (6mCCD) - Pooled Data

End point title	6-month confirmed disability worsening (6mCDW) or 6-month confirmed cognitive decline (6mCCD) - Pooled Data

End point description:

A 6-month confirmed disability worsening (6mCDW) was defined as an increase from baseline in Expanded Disability Status Scale (EDSS) score sustained for at least 6 months. For patients with a baseline EDSS of 0, the criterion for disability worsening was an increase in EDSS of ≥1.5, for patients with a baseline EDSS of 1 to 5 or ≥5.5, the criterion for disability worsening was an increase in EDSS of ≥1 or ≥0.5, respectively. A 6-month confirmed cognitive decline (6mCCD) was defined as a 4-point worsening on Symbol Digit Modalities Test (SDMT) sustained for at least 6 months. This study was not powered for the analysis of this endpoint individually. It was pre-specified in the study protocol to combine the data from this study with study COMB157G2301 to address this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to 2.5 years

End point values	OMB 20 mg - Pooled	TER 14 mg - Pooled		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	941	930		
Units: percentage of participants				
number (confidence interval 95%)				
Month 18 - from Kaplan Meier estimates	20.5 (18.0 to 23.4)	21.7 (19.1 to 24.6)		
Month 24 - from Kaplan Meier estimates	21.4 (18.8 to 24.3)	22.6 (19.9 to 25.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in cognitive performance measured by the Symbol Digit Modalities Test (SDMT) - Pooled Data

End point title	Change in cognitive performance measured by the Symbol Digit Modalities Test (SDMT) - Pooled Data

End point description:

Processing speed is being measured by the Symbol Digit Modalities Test (SDMT) score. SDMT measures the time to pair abstract symbols with specific numbers. The test requires visuoperceptual processing, working memory, and psychomotor speed. The score is the number of correctly coded items in 90 seconds. (max=110, min=0). Higher scores indicate improvement. Lower scores indicate worsening. This study was not powered for the analysis of this endpoint individually. It was pre-specified in the study protocol to combine the data from this study with study COMB157G2301 to address this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to 2.5 years

End point values	OMB 20 mg - Pooled	TER 14 mg - Pooled		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	921	909		
Units: scores				
arithmetic mean (confidence interval 95%)				
Month 6 n=921,909	1.02 (0.46 to 1.59)	0.64 (0.07 to 1.20)		
Month 12 n=879,863	1.82 (1.22 to 2.41)	1.70 (1.10 to 2.30)		
Month 18 n=849,808	2.84 (2.24 to 3.45)	2.05 (1.44 to 2.67)		
Month 24 n=492,468	3.50 (2.80 to 4.20)	2.39 (1.67 to 3.11)		
Month 30 n=156,117	3.53 (2.39 to 4.68)	2.97 (1.67 to 4.28)		

Statistical analyses

No statistical analyses for this end point

Secondary: 6-month confirmed worsening of at least 20% in the Timed 25-Foot Walk (T25FW) - Pooled Data

End point title	6-month confirmed worsening of at least 20% in the Timed 25-

	Foot Walk (T25FW) - Pooled Data

End point description:

The patient is directed to walk 25 feet quickly and safely as possible from one marked end to the other. The time is calculated from the initiation of the patient instructed to begin, until the patient has reached the 25-foot mark. This study was not powered for the analysis of this endpoint individually. It was pre-specified in the study protocol to combine the data from this study with study COMB157G2301 to address this endpoint.

End point type	Secondary

End point timeframe:

Baseline, every 3 months up to 2.5 years

End point values	OMB 20 mg - Pooled	TER 14 mg - Pooled		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	936	925		
Units: percentage of participants				
number (confidence interval 95%)				
Month 18 - from Kaplan Meier estimates	11.0 (9.1 to 13.3)	10.4 (8.5 to 12.6)		
Month 24 - from Kaplan Meier estimates	11.4 (9.5 to 13.8)	10.6 (8.7 to 12.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: 6-month confirmed worsening of at least 20% in the 9-Hole Peg Test (9HPT) - Pooled Data

End point title	6-month confirmed worsening of at least 20% in the 9-Hole Peg Test (9HPT) - Pooled Data

End point description:

9 Hole Peg Test is a test of upper limb function. Participants place 9 pegs on pegboard and remove pegs and this is timed for each hand. Time recorded in seconds. Longer time indicates poorer upper limb function. 20% improvement is defined as 20% shorter time in seconds. This study was not powered for the analysis of this endpoint individually. It was pre-specified in the study protocol to combine the data from this study with study COMB157G2301 to address this endpoint.

End point type	Secondary

End point timeframe:

Baseline, every 6 months up to 2.5 years

End point values	OMB 20 mg - Pooled	TER 14 mg - Pooled		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	932	920		
Units: percentage of participants				
number (confidence interval 95%)				
Month 18 - from Kaplan Meier estimates	2.9 (2.0 to 4.3)	3.3 (2.3 to 4.8)		
Month 24 - from Kaplan Meier estimates	2.9 (2.0 to 4.3)	3.3 (2.3 to 4.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: 6-month confirmed disability improvement (6mCDI) sustained until End of Study (EOS) as measured by EDSS - Pooled Data

End point title	6-month confirmed disability improvement (6mCDI) sustained until End of Study (EOS) as measured by EDSS - Pooled Data

End point description:

A 6-month confirmed disability improvement (6mCDI) sustained until EOS was defined as a decrease from baseline EDSS sustained until EOS. For patients with a baseline EDSS of 0 to 1.5, no disability improvement was possible based on the protocol definition of an improvement; for patients with a baseline EDSS of ≥2 to 6 or ≥6.5 to 9.5, the criterion for disability improvement was a decrease in EDSS of ≤1 or ≤0.5, respectively. This study was not powered for the analysis of this endpoint individually. It was pre-specified in the study protocol to combine the data from this study with study COMB157G2301 to address this endpoint.

End point type	Secondary

End point timeframe:

Baseline, every 3 months up to 2.5 years

End point values	OMB 20 mg - Pooled	TER 14 mg - Pooled		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	749	724		
Units: percentage of participants				
number (confidence interval 95%)				
Month 18 - from Kaplan Meier estimates	5.4 (4.0 to 7.4)	4.6 (3.2 to 6.5)		
Month 24 - from Kaplan Meier estimates	5.8 (4.2 to 7.8)	4.6 (3.2 to 6.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of new or enlarging T2 lesions on MRI per year from Month 12 until End of Study (EOS)

End point title	Number of new or enlarging T2 lesions on MRI per year from Month 12 until End of Study (EOS)

End point description:

Number of new/enlarging T2 lesions on the last available MRI scan compared to Month 12 adjusted for different time of scans versus Month 12 due to variable follow up time in study.

End point type	Secondary

End point timeframe:

Month 12 up to 2.5 years

End point values	OMB 20 mg	TER 14 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	369	348		
Units: T2 lesions per year				
arithmetic mean (confidence interval 95%)	0.13 (0.09 to 0.18)	3.84 (3.19 to 4.62)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in T2 lesion volume relative to baseline

End point title	Percent change in T2 lesion volume relative to baseline

End point description:

Percent change from baseline in total T2 lesion volume

End point type	Secondary

End point timeframe:

Baseline, Month 12, Month 24

End point values	OMB 20 mg	TER 14 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	447	437		
Units: percentage change in lesion volume				
arithmetic mean (standard deviation)				
Month 12 n=447,437	-2.4 (± 8.66)	10.1 (± 38.57)		
Month 24 n=330,320	-2.6 (± 9.34)	17.8 (± 53.48)		

Statistical analyses

No statistical analyses for this end point

Secondary: No evidence of disease activity (NEDA-4)

End point title	No evidence of disease activity (NEDA-4)

End point description:

NEDA-4 was defined as no 3-month confirmed disability worsening, no confirmed MS relapse, no new or enlarging T2 lesions compared to baseline, and the annualized rate of brain atrophy >-0.04%.

End point type	Secondary

End point timeframe:

Baseline, Month 12, Month 24

End point values	OMB 20 mg	TER 14 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	433	427		
Units: percentage of participants				
number (confidence interval 95%)				
Month 12 n=433,427	23.8 (19.8 to 27.8)	17.8 (14.2 to 21.4)		
Month 24 n=92,78	9.8 (3.7 to 15.9)	5.1 (0.2 to 10.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Multiple Sclerosis Impact Scale (MSIS-29) physical impact score change from baseline

End point title	Multiple Sclerosis Impact Scale (MSIS-29) physical impact score change from baseline

End point description:

MSIS-29 is a 29-item, self-administered questionnaire that includes 2 domains, physical and psychological. Responses are captured on a 4-point scale ranging from "not at all" (1) to "extremely" (4), where higher scores reflect greater impact on day to day life.

End point type	Secondary

End point timeframe:

Baseline, every 6 months up to 2.5 years

End point values	OMB 20 mg	TER 14 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	473	461		
Units: scores on a scale				
arithmetic mean (standard error)				
Month 6 n=473,461	-2.20 (± 0.652)	-0.46 (± 0.659)		
Month 12 n=448,438	-2.47 (± 0.698)	-0.49 (± 0.704)		
Month 18 n=425,409	-2.29 (± 0.784)	1.53 (± 0.794)		
Month 24 n=235,238	-2.93 (± 0.904)	0.62 (± 0.905)		
Month 30 n=70,54	-2.49 (± 1.270)	1.44 (± 1.397)		

Statistical analyses

No statistical analyses for this end point

Secondary: Multiple Sclerosis Impact Scale (MSIS-29) psychological impact score change from baseline

End point title	Multiple Sclerosis Impact Scale (MSIS-29) psychological impact score change from baseline

End point description:

MSIS-29 is a 29-item, self-administered questionnaire that includes 2 domains, physical and psychological. Responses are captured on a 4-point scale ranging from "not at all" (1) to "extremely" (4), where higher scores reflect greater impact on day to day life.

End point type	Secondary

End point timeframe:

Baseline, every 6 months up to 2.5 years

End point values	OMB 20 mg	TER 14 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	473	461		
Units: scores on a scale				
arithmetic mean (standard error)				
Month 6 n=473,461	-5.96 (± 0.807)	-3.77 (± 0.816)		
Month 12 n=448,436	-5.42 (± 0.830)	-3.88 (± 0.839)		
Month 18 n=423,409	-6.23 (± 0.884)	-2.51 (± 0.896)		
Month 24 n=234,238	-6.10 (± 1.092)	-3.12 (± 1.090)		
Month 30 n=70,54	-6.25 (± 1.623)	-4.75 (± 1.797)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized relapse rates (ARR) by NfL high-low subgroups - Pooled Data

End point title	Annualized relapse rates (ARR) by NfL high-low subgroups - Pooled Data

End point description:

ARR was the number of confirmed relapses in a year, calculated as the total number of relapses for all participants in the treatment group divided by the total participant-years of time in study. A confirmed MS relapse was defined as one accompanied by a clinically-relevant change in the EDSS performed by the Independent EDSS rater, i.e. an increase of at least 0.5 points on the EDSS score, or an increase of 1 point on two functional scores or 2 points on one functional score (excluding changes involving bowel/bladder or cerebral functional system).

End point type	Secondary

End point timeframe:

Baseline up to 2.5 years

End point values	OMB 20 mg - Pooled	TER 14 mg - Pooled		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	871	841		
Units: number of relapses in a year				
arithmetic mean (confidence interval 95%)				
High > median n=443,410	0.08 (0.07 to 0.11)	0.21 (0.17 to 0.26)		
Low <= median n=428,431	0.12 (0.09 to 0.15)	0.23 (0.19 to 0.27)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of new or enlarging T2 lesions per year by NfL high-low subgroups - Pooled Data

End point title	Number of new or enlarging T2 lesions per year by NfL high-low subgroups - Pooled Data
End point description:	
Number of new or enlarging T2 lesions on MRI per year (annualized lesion rate).	
End point type	Secondary
End point timeframe:	
Baseline, yearly up to 2.5 years	

End point values	OMB 20 mg - Pooled	TER 14 mg - Pooled		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	850	823		
Units: T2 lesions per year				
arithmetic mean (confidence interval 95%)				
High > median n=432,402	0.95 (0.82 to 1.11)	5.28 (4.61 to 6.03)		
Low <= median n=418,421	0.39 (0.33 to 0.47)	3.02 (2.64 to 3.46)		

Statistical analyses

No statistical analyses for this end point

Secondary: Brain volume loss by NfL high-low subgroups - Pooled Data

End point title	Brain volume loss by NfL high-low subgroups - Pooled Data

End point description:

Percent change from baseline in brain volume loss (BVL) on all MRI scans adjusted for different time of scan versus baseline due to variable follow up time in study.

End point type	Secondary

End point timeframe:

Baseline, Months 12 and 24

End point values	OMB 20 mg - Pooled	TER 14 mg - Pooled		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	819	794		
Units: percentage of brain volume loss				
arithmetic mean (confidence interval 95%)				
High > median n=416,387	-0.32 (-0.38 to -0.26)	-0.43 (-0.49 to -0.37)		
Low <= median n=403,407	-0.24 (-0.30 to -0.18)	-0.29 (-0.35 to -0.22)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) concentrations of ofatumumab

End point title	Pharmacokinetic (PK) concentrations of ofatumumab[1]

End point description:

Summary statistics of pharmacokinetic (PK) concentrations from trough samples collected within a 7-day window prior or at day of dosing.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 12, 24, 48, 96

Notes:

[1] - 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: No analysis was done

End point values	OMB 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	481			
Units: ug/mL				
arithmetic mean (standard deviation)				
Baseline n=325	0.00325 (± 0.031372)			
Week 4 n=346	1.26512 (± 0.964645)			
Week 12 n=257	0.20932 (± 0.287839)			
Week 24 n=243	0.38203 (± 0.433175)			

Week 48 n=240 Week 96 n=304	0.59087 (± 0.594490) 1.13218 (± 0.991141)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were reported from first dose of study treatment until last administration of study treatment plus 100 days post treatment, up to maximum duration of approximately 2.7 years.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups	
Reporting group title	TER 14 mg
Reporting group description:	
Teriflunomide 14 mg capsule orally once daily (+ ofatumumab-matching placebo injections on Days 1, 7, 14, Week 4 and every 4 weeks thereafter)	
Reporting group title	OMB 20 mg
Reporting group description:	
Ofatumumab 20 mg s.c. injections on Days 1, 7, 14, Week 4 and every 4 weeks thereafter (+ teriflunomide-matching placebo capsule orally once daily)	

Serious adverse events	TER 14 mg	OMB 20 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	37 / 474 (7.81%)	42 / 481 (8.73%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 474 (0.21%)	2 / 481 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibroadenoma of breast			
subjects affected / exposed	0 / 474 (0.00%)	1 / 481 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	1 / 474 (0.21%)	2 / 481 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign breast neoplasm			

subjects affected / exposed	0 / 474 (0.00%)	1 / 481 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic dissection			
subjects affected / exposed	1 / 474 (0.21%)	0 / 481 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 474 (0.21%)	1 / 481 (0.21%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Drug withdrawal syndrome			
subjects affected / exposed	0 / 474 (0.00%)	1 / 481 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 474 (0.21%)	0 / 481 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 474 (0.00%)	1 / 481 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 474 (0.21%)	0 / 481 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Testicular infarction			

subjects affected / exposed	0 / 474 (0.00%)	1 / 481 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine haemorrhage			
subjects affected / exposed	1 / 474 (0.21%)	0 / 481 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine polyp			
subjects affected / exposed	2 / 474 (0.42%)	0 / 481 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterovaginal prolapse			
subjects affected / exposed	1 / 474 (0.21%)	0 / 481 (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			
Pulmonary embolism			
subjects affected / exposed	1 / 474 (0.21%)	0 / 481 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sarcoidosis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 481 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 474 (0.21%)	0 / 481 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 474 (0.21%)	0 / 481 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Major depression			
subjects affected / exposed	1 / 474 (0.21%)	0 / 481 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	0 / 474 (0.00%)	1 / 481 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	1 / 474 (0.21%)	0 / 481 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 474 (0.00%)	2 / 481 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone contusion			
subjects affected / exposed	1 / 474 (0.21%)	0 / 481 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	0 / 474 (0.00%)	1 / 481 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	1 / 474 (0.21%)	0 / 481 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 474 (0.21%)	1 / 481 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Femoral neck fracture			
subjects affected / exposed	1 / 474 (0.21%)	0 / 481 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 474 (0.21%)	0 / 481 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 474 (0.00%)	1 / 481 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	1 / 474 (0.21%)	0 / 481 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 474 (0.00%)	1 / 481 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			
subjects affected / exposed	1 / 474 (0.21%)	0 / 481 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	1 / 474 (0.21%)	0 / 481 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural inflammation			
subjects affected / exposed	1 / 474 (0.21%)	0 / 481 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			

subjects affected / exposed	1 / 474 (0.21%)	0 / 481 (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	0 / 474 (0.00%)	1 / 481 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 474 (0.00%)	1 / 481 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon injury			
subjects affected / exposed	0 / 474 (0.00%)	1 / 481 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 474 (0.00%)	1 / 481 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Bundle branch block bilateral			
subjects affected / exposed	0 / 474 (0.00%)	1 / 481 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 474 (0.21%)	0 / 481 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 474 (0.00%)	1 / 481 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nodal arrhythmia			

subjects affected / exposed	0 / 474 (0.00%)	1 / 481 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 474 (0.00%)	2 / 481 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar radiculopathy			
subjects affected / exposed	1 / 474 (0.21%)	0 / 481 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis			
subjects affected / exposed	1 / 474 (0.21%)	0 / 481 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis relapse			
subjects affected / exposed	1 / 474 (0.21%)	1 / 481 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelopathy			
subjects affected / exposed	1 / 474 (0.21%)	0 / 481 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 474 (0.00%)	2 / 481 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigeminal neuralgia			
subjects affected / exposed	0 / 474 (0.00%)	1 / 481 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Quadriparesis			

subjects affected / exposed	0 / 474 (0.00%)	1 / 481 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 474 (0.21%)	0 / 481 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 474 (0.00%)	1 / 481 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 481 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 474 (0.21%)	0 / 481 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 474 (0.00%)	1 / 481 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	0 / 474 (0.00%)	1 / 481 (0.21%)	
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 / 474 (0.21%)	0 / 481 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cholelithiasis			
subjects affected / exposed	0 / 474 (0.00%)	2 / 481 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 474 (0.21%)	0 / 481 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 474 (0.00%)	1 / 481 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 474 (0.00%)	1 / 481 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lichen sclerosus			
subjects affected / exposed	1 / 474 (0.21%)	0 / 481 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 474 (0.21%)	0 / 481 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc compression			
subjects affected / exposed	0 / 474 (0.00%)	1 / 481 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			

subjects affected / exposed	1 / 474 (0.21%)	1 / 481 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	0 / 474 (0.00%)	1 / 481 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 474 (0.21%)	0 / 481 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylitis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 481 (0.21%)	
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	1 / 474 (0.21%)	5 / 481 (1.04%)	
occurrences causally related to treatment / all	0 / 1	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 474 (0.21%)	0 / 481 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 481 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 474 (0.00%)	1 / 481 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			

subjects affected / exposed	0 / 474 (0.00%)	1 / 481 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 474 (0.21%)	0 / 481 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paronychia			
subjects affected / exposed	1 / 474 (0.21%)	0 / 481 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 474 (0.21%)	0 / 481 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 474 (0.00%)	1 / 481 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative abscess			
subjects affected / exposed	1 / 474 (0.21%)	0 / 481 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	0 / 474 (0.00%)	1 / 481 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 474 (0.21%)	0 / 481 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	2 / 474 (0.42%)	2 / 481 (0.42%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 481 (0.21%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 474 (0.21%)	0 / 481 (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	TER 14 mg	OMB 20 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	322 / 474 (67.93%)	348 / 481 (72.35%)	
Investigations			
Blood immunoglobulin M decreased			
subjects affected / exposed	8 / 474 (1.69%)	31 / 481 (6.44%)	
occurrences (all)	10	42	
Injury, poisoning and procedural complications			
Injection related reaction			
subjects affected / exposed	66 / 474 (13.92%)	119 / 481 (24.74%)	
occurrences (all)	148	203	
Vascular disorders			
Hypertension			
subjects affected / exposed	32 / 474 (6.75%)	20 / 481 (4.16%)	
occurrences (all)	34	22	
Nervous system disorders			
Headache			
subjects affected / exposed	66 / 474 (13.92%)	69 / 481 (14.35%)	
occurrences (all)	87	128	
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	32 / 474 (6.75%)	25 / 481 (5.20%)	
occurrences (all)	36	25	
Injection site reaction			
subjects affected / exposed	26 / 474 (5.49%)	61 / 481 (12.68%)	
occurrences (all)	46	318	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	49 / 474 (10.34%)	28 / 481 (5.82%)	
occurrences (all)	56	31	
Nausea			
subjects affected / exposed	32 / 474 (6.75%)	30 / 481 (6.24%)	
occurrences (all)	43	39	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	24 / 474 (5.06%)	17 / 481 (3.53%)	
occurrences (all)	29	20	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	75 / 474 (15.82%)	27 / 481 (5.61%)	
occurrences (all)	78	27	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	17 / 474 (3.59%)	30 / 481 (6.24%)	
occurrences (all)	22	33	
Depression			
subjects affected / exposed	24 / 474 (5.06%)	23 / 481 (4.78%)	
occurrences (all)	26	26	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	30 / 474 (6.33%)	22 / 481 (4.57%)	
occurrences (all)	35	28	
Arthralgia			
subjects affected / exposed	25 / 474 (5.27%)	30 / 481 (6.24%)	
occurrences (all)	30	35	
Back pain			

subjects affected / exposed	24 / 474 (5.06%)	35 / 481 (7.28%)	
occurrences (all)	26	36	
Infections and infestations			
Influenza			
subjects affected / exposed	28 / 474 (5.91%)	27 / 481 (5.61%)	
occurrences (all)	29	32	
Nasopharyngitis			
subjects affected / exposed	88 / 474 (18.57%)	88 / 481 (18.30%)	
occurrences (all)	132	149	
Upper respiratory tract infection			
subjects affected / exposed	47 / 474 (9.92%)	52 / 481 (10.81%)	
occurrences (all)	62	68	
Urinary tract infection			
subjects affected / exposed	34 / 474 (7.17%)	55 / 481 (11.43%)	
occurrences (all)	40	81	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 January 2017	Amendment 1 was created at the request of several Health Authorities to provide additional guidance to the Investigators in regards to: switching to alternative disease modifying therapy for patients that have discontinued study drug and re-evaluation of benefit/risk of continuing study drug in patients, who experienced relevant progression of their disease (met criterion for 6-month confirmed disease worsening) while on study treatment.
06 August 2018	Amendment 2 was created to update the secondary objectives of the study and to provide clarification of the rescreening of patients. Modifications to the secondary objectives included: addition of endpoints related to NfL as secondary objectives and additional endpoint related to cognitive decline as measured on the SDMT, addition of composite endpoint related to physical disability and cognition, as measured by disability worsening on EDSS and cognitive decline on SDMT.

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.

This study was not powered for the analysis of some secondary endpoints as a stand-alone study. It was pre-specified in the study protocol to combine the data with study COMB157G2301 to address these endpoints.

Notes: