EU Clinical Trials Register

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	2015-005418-31
Trial protocol	BE DE HU GB SE DK CZ SK ES NL EE BG GR PL HR FR IT
Global end of trial date	20 July 2020

Results information

Result version number	v1 (current)
This version publication date	05 August 2021
First version publication date	05 August 2021

Trial information

Trial identification

Sponsor protocol code	COMB157G2301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02792218
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	20 July 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective was to demonstrate that ofatumumab 20 mg subcutaneous injection once every 4 weeks was superior to teriflunomide 14 mg given orally, once daily, in reducing the frequency of confirmed relapses as evaluated by the annualized relapse rate (ARR) in patients with relapsing multiple sclerosis.

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	20 September 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: 18
Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Bulgaria: 15
Country: Number of subjects enrolled	Canada: 15
Country: Number of subjects enrolled	Croatia: 16
Country: Number of subjects enrolled	Czechia: 36
Country: Number of subjects enrolled	Denmark: 17
Country: Number of subjects enrolled	Estonia: 18
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Germany: 31
Country: Number of subjects enrolled	Greece: 9
Country: Number of subjects enrolled	Hungary: 18
Country: Number of subjects enrolled	India: 29
Country: Number of subjects enrolled	Israel: 11
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Mexico: 8
Country: Number of subjects enrolled	Netherlands: 15

Country: Number of subjects enrolled	Poland: 197
Country: Number of subjects enrolled	Russian Federation: 153
Country: Number of subjects enrolled	Slovakia: 12
Country: Number of subjects enrolled	Spain: 54
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	Thailand: 1
Country: Number of subjects enrolled	Turkey: 13
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	United States: 193
Worldwide total number of subjects	927
EEA total number of subjects	475

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)	927
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 1277 patients were screened, of whom 927 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, Carer, Data analyst, 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	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

Investigational medicinal product name	Teriflunomide-matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo (teriflunomide 0 mg) capsule orally once daily

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

Dosage and administration details:

Placebo (OMB 0 mg) pre-filled syringes for subcutaneous injection on days 1 ,7 ,14,Week 4 and every 4 weeks thereafter

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

Number of subjects in period 1	OMB 20 mg	TER 14 mg
Started	465	462
Completed	416	381
Not completed	49	81
Physician decision	4	4
Adverse event, non-fatal	15	14
Protocol deviation	3	2
Non-compliance with study treatment	-	1
Pregnancy	1	-
Patient/guardian decision	15	42
Lost to follow-up	10	5
New therapy for study indication	-	1
Lack of efficacy	1	12

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	465	462	927
Age categorical			
Units: Subjects			
Adults (18-64 years)	465	462	927
Age Continuous			
Units: Years			
arithmetic mean	38.9	37.8	
standard deviation	± 8.77	± 8.95	-
Sex: Female, Male			
Units: Participants			
Female	318	317	635
Male	147	145	292
Race/Ethnicity, Customized			
Units: Subjects			
Asian	15	16	31
Black or African American	15	20	35
White	411	412	823
Other	22	14	36
Unknown	2	0	2
Number of relapses in the past 12 months prior to screening			
Reported numbers are from investigator records			
Units: Number of relapses			
arithmetic mean	1.2	1.3	
standard deviation	± 0.63	± 0.69	-
Expanded Disability Status Scale (EDSS)			
Units: Score on a scale			
arithmetic mean	2.97	2.94	
standard deviation	± 1.357	± 1.355	-
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	1.7	1.2	
standard deviation	± 4.93	± 2.58	-

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)	

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	454	451		
Units: number of relapses in a year				
arithmetic mean (confidence interval 95%)	0.11 (0.09 to 0.14)	0.22 (0.18 to 0.26)		

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	905
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	negative binomial regression model
Parameter estimate	rate ratio
Point estimate	0.495
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.375
upper limit	0.655

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

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

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 COMB157G2302 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	465	459		
Units: percentage of participants				
number (confidence interval 95%)				
Month 18 - from Kaplan Meier estimates	9.4 (7.0 to 12.6)	13.9 (10.9 to 17.5)		
Month 24 - from Kaplan Meier estimates	11.3 (8.4 to 15.1)	15.4 (12.1 to 19.4)		

Statistical analyses

Statistical analysis title	3mCDW

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 COMB157G2302 to address this endpoint.

Comparison groups	OMB 20 mg v TER 14 mg

Number of subjects included in analysis	924
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.029
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.652
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.445
upper limit	0.956

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

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

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 COMB157G2302 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	465	459		
Units: percentage of participants				
number (confidence interval 95%)				
Month 18- from Kaplan Meier estimates	7.5 (5.4 to 10.4)	11.5 (8.9 to 14.9)		
Month 24 - from Kaplan Meier estimates	8.2 (6.0 to 11.3)	13.0 (10.0 to 16.9)		

Statistical analyses

Statistical analysis title	6mCDW

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 COMB157G2302 to address this endpoint.

Comparison groups	OMB 20 mg v TER 14 mg

Number of subjects included in analysis	924
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.022
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.607
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.396
upper limit	0.93

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

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

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 COMB157G2302 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	375	363		
Units: percentage of participants				
arithmetic mean (confidence interval 95%)				
Month 18 - from Kaplan Meier estimates	9.1 (6.5 to 12.7)	7.1 (4.8 to 10.3)		
Month 24 - from Kaplan Meier estimates	9.7 (7.0 to 13.5)	8.2 (5.6 to 11.9)		

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 COMB157G2302 to address this endpoint.

Comparison groups	OMB 20 mg v TER 14 mg

Number of subjects included in analysis	738
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.516
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.186
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.709
upper limit	1.983

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

End point title	Number of Gd-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	432	420		
Units: lesions per scan				
arithmetic mean (confidence interval 95%)	0.0115 (0.006 to 0.022)	0.4555 (0.358 to 0.579)		

Statistical analyses

Statistical analysis title	T1 lesions
Comparison groups	OMB 20 mg v TER 14 mg
Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	negative binomial regression model
Parameter estimate	rate ratio
Point estimate	0.025

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.013
upper limit	0.049

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	440	431		
Units: T2 lesions per year				
arithmetic mean (confidence interval 95%)				
Month 12 n=420,407	1.13 (0.95 to 1.33)	4.30 (3.71 to 4.98)		
Month 24 n=103,93	0.72 (0.53 to 0.98)	3.21 (2.42 to 4.24)		
EOS n=440,431	0.72 (0.61 to 0.85)	4.00 (3.47 to 4.61)		

Statistical analyses

Statistical analysis title	T2 lesions

Statistical analysis description:

Month 12

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	0.26

Confidence interval

level	95 %
sides	2-sided
lower limit	0.21
upper limit	0.33

Statistical analysis title	T2 lesions

Statistical analysis description:

Month 24

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	0.22

Confidence interval

level	95 %
sides	2-sided
lower limit	0.15
upper limit	0.34

Statistical analysis title	T2 lesions

Statistical analysis description:

End of Study

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	0.18

Confidence interval

level	95 %
sides	2-sided
lower limit	0.15
upper limit	0.22

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	430	403		
Units: pg/mL				
geometric mean (confidence interval 95%)				
Month 3 n=430,403	8.80 (8.48 to 9.13)	9.41 (9.06 to 9.77)		
Month 12 n=414,398	7.02 (6.73 to 7.32)	9.63 (9.23 to 10.06)		
Month 24 n=371,349	6.90 (6.57 to 7.24)	8.99 (8.56 to 9.45)		

Statistical analyses

Statistical analysis title	NfL
Statistical analysis description:	
Month 3	
Comparison groups	OMB 20 mg v TER 14 mg
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.011
Method	Mixed models analysis
Parameter estimate	Geo-mean ratio
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	0.98

Statistical analysis title	NfL
Statistical analysis description:	
Month 12	
Comparison groups	OMB 20 mg v TER 14 mg

Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Geo-mean ratio
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	0.77

Statistical analysis title	NfL
Statistical analysis description:	
Month 24	
Comparison groups	OMB 20 mg v TER 14 mg
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Geo-mean ratio
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	0.82

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	418	408		
Units: percentage of brain volume loss				
arithmetic mean (confidence interval 95%)	-0.28 (-0.34 to 0.22)	-0.35 (-0.41 to 0.29)		

Statistical analyses

Statistical analysis title	Brain volume
Comparison groups	OMB 20 mg v TER 14 mg
Number of subjects included in analysis	826
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.118
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: Time to first confirmed relapse

End point title	Time to first 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	454	451		
Units: percentage of participants				
number (confidence interval 95%)	18.82 (15.27 to 23.09)	32.73 (27.95 to 38.09)		

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	453	448		
Units: number of relapses in a year				
arithmetic mean (confidence interval 95%)	0.096 (0.05 to 0.14)	0.242 (0.17 to 0.31)		

Statistical analyses

No statistical analyses for this end point

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

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

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 COMB157G2302 to address this endpoint.

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	0[1]	0[2]		
Units: percentage of participants				
number (confidence interval 95%)	(to)	(to)		

Notes:

[1] - Pre-specified in protocol that data for this outcome will be combined with study COMB157G2302.

[2] - Pre-specified in protocol that data for this outcome will be combined with study COMB157G2302.

Statistical analyses

No statistical analyses for this end point

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

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

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 COMB157G2302 to address this endpoint.

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	0[3]	0[4]		
Units: scores				
number (confidence interval 95%)	(to)	(to)		

Notes:

[3] - Pre-specified in protocol that data for this outcome will be combined with study COMB157G2302.

[4] - Pre-specified in protocol that data for this outcome will be combined with study COMB157G2302.

Statistical analyses

No statistical analyses for this end point

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

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

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 COMB157G2302 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	TER 14 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[5]	0[6]		
Units: percentage of participants				
number (confidence interval 95%)	(to)	(to)		

Notes:

[5] - Pre-specified in protocol that data for this outcome will be combined with study COMB157G2302.

[6] - Pre-specified in protocol that data for this outcome will be combined with study COMB157G2302.

Statistical analyses

No statistical analyses for this end point

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

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

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 COMB157G2302 to address this endpoint.

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	0[7]	0[8]		
Units: percentage of participants				
number (confidence interval 95%)	(to)	(to)		

Notes:

[7] - Pre-specified in protocol that data for this outcome will be combined with study COMB157G2302.

[8] - Pre-specified in protocol that data for this outcome will be combined with study COMB157G2302.

Statistical analyses

No statistical analyses for this end point

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

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

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.

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	0[9]	0[10]		
Units: percentage of participants				
number (confidence interval 95%)	(to)	(to)		

Notes:

[9] - Pre-specified in protocol/SAP that data for this outcome will be combined with study COMB157G2302.

[10] - Pre-specified in protocol/SAP that data for this outcome will be combined with study COMB157G2302.

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)

End point title	6-month confirmed worsening of at least 20% in the Timed 25-Foot Walk (T25FW)

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 COMB157G2302 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	0[11]	0[12]		
Units: percentage of participants				
number (confidence interval 95%)	(to)	(to)		

Notes:

[11] - Pre-specified in protocol that data for this outcome will be combined with study COMB157G2302.

[12] - Pre-specified in protocol that data for this outcome will be combined with study COMB157G2302.

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)

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

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 COMB157G2302 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	TER 14 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[13]	0[14]		
Units: percentage of participants				
number (confidence interval 95%)	(to)	(to)		

Notes:

[13] - Pre-specified in protocol that data for this outcome will be combined with study COMB157G2302.

[14] - Pre-specified in protocol that data for this outcome will be combined with study COMB157G2302.

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

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

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 COMB157G2302 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	0[15]	0[16]		
Units: percentage of participants				
number (confidence interval 95%)	(to)	(to)		

Notes:

[15] - Pre-specified in protocol that data for this outcome will be combined with study COMB157G2302.

[16] - Pre-specified in protocol that data for this outcome will be combined with study COMB157G2302.

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	356	344		
Units: T2 lesions per year				
arithmetic mean (confidence interval 95%)	0.05 (0.03 to 0.09)	3.73 (3.12 to 4.46)		

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	436	430		
Units: percentage change in lesion volume				
arithmetic mean (standard deviation)				
Month 12 n=436,430	-1.4 (± 14.07)	9.7 (± 28.83)		
Month 24 n=332,324	-2.6 (± 10.48)	13.5 (± 34.71)		

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	428	413		
Units: percentage of participants				
number (confidence interval 95%)				
Month 12 n=428,413	23.4 (19.4 to 27.4)	14.8 (11.3 to 18.2)		
Month 24 n=104,95	14.4 (7.7 to 21.2)	3.2 (0.0 to 6.7)		

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	455	451		
Units: scores on a scale				
arithmetic mean (standard error)				
Month 6 n=455,451	-2.75 (± 0.687)	-0.44 (± 0.690)		
Month 12 n=438,428	-2.43 (± 0.704)	0.17 (± 0.710)		
Month 18 n=428,406	-2.37 (± 0.768)	0.67 (± 0.780)		
Month 24 n=262,233	-2.60 (± 0.842)	0.59 (± 0.874)		
Month 30 n=86,65	-3.16 (± 1.130)	0.57 (± 1.262)		

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	455	451		
Units: scores on a scale				
arithmetic mean (standard error)				

Month 6 n=454,449	-5.20 (± 0.835)	-3.07 (± 0.839)		
Month 12 n=438,427	-5.22 (± 0.902)	-2.57 (± 0.910)		
Month 18 n=428,406	-5.72 (± 0.919)	-3.94 (± 0.937)		
Month 24 n=262,232	-6.14 (± 0.972)	-3.93 (± 1.013)		
Month 30 n=86,65	-7.78 (± 1.509)	-0.85 (± 1.698)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Annualized relapse rates (ARR) by NfL high-low subgroups
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	TER 14 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[17]	0[18]		
Units: number of relapses in a year				
arithmetic mean (confidence interval 95%)	(to)	(to)		

Notes:

[17] - Supportive sub-group analysis based on estimations from pooled data from this study and COMB157G2302

[18] - Supportive sub-group analysis based on estimations from pooled data from this study and COMB157G2302

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of new or enlarging T2 lesions per year by NfL high-low subgroups
End point description:	

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

End point type	Secondary

End point values	OMB 20 mg	TER 14 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[19]	0[20]		
Units: T2 lesions per year				
arithmetic mean (confidence interval 95%)	(to)	(to)		

Notes:

[19] - Supportive sub-group analysis based on estimations from pooled data from this study and COMB157G2302

[20] - Supportive sub-group analysis based on estimations from pooled data from this study and COMB157G2302

Statistical analyses

No statistical analyses for this end point

Secondary: Brain volume loss by NfL high-low subgroups

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

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	0[21]	0[22]		
Units: percentage of brain volume loss				
arithmetic mean (confidence interval 95%)	(to)	(to)		

Notes:

[21] - Supportive sub-group analysis based on estimations from pooled data from this study and COMB157G2302

[22] - Supportive sub-group analysis based on estimations from pooled data from this study and COMB157G2302

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) concentrations of ofatumumab

End point title	Pharmacokinetic (PK) concentrations of ofatumumab[23]

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:

[23] - 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	465			
Units: ug/mL				
arithmetic mean (standard deviation)				
Baseline n=304	0.00267 (± 0.033819)			
Week 4 n=347	1.25746 (± 0.985148)			
Week 12 n=323	0.22645 (± 0.339619)			
Week 24 n=304	0.36991 (± 0.437480)			
Week 48 n=270	0.51280 (± 0.463758)			
Week 96 n=336	1.05314 (± 0.992612)			

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 end of study treatment plus 100 days post treatment, up to a maximum duration of 2.7 years.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	OMB 20mg
Reporting group description:	
OMB 20mg	
Reporting group title	TER 14mg
Reporting group description:	
TER 14mg	

Serious adverse events	OMB 20mg	TER 14mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	51 / 465 (10.97%)	39 / 462 (8.44%)	
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)			
Cervix carcinoma			
subjects affected / exposed	0 / 465 (0.00%)	1 / 462 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibrosarcoma			
subjects affected / exposed	0 / 465 (0.00%)	1 / 462 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive breast carcinoma			
subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma in situ			

subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Hodgkin's lymphoma recurrent			
subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Thrombophlebitis			
subjects affected / exposed	0 / 465 (0.00%)	1 / 462 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Adnexa uteri cyst			
subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical dysplasia			

subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Menorrhagia		
subjects affected / exposed	1 / 465 (0.22%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Metrorrhagia		
subjects affected / exposed	0 / 465 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Uterine polyp		
subjects affected / exposed	0 / 465 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders		
Pneumonia aspiration		
subjects affected / exposed	0 / 465 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pulmonary embolism		
subjects affected / exposed	0 / 465 (0.00%)	2 / 462 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Pulmonary sarcoidosis		
subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Psychiatric disorders		
Depression		
subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Depression suicidal			
subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somatic symptom disorder			
subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress			
subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (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	2 / 465 (0.43%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Liver function test increased			
subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric evaluation			

subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Weight decreased		
subjects affected / exposed	0 / 465 (0.00%)	1 / 462 (0.22%)
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		
Fibula fracture		
subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Injection related reaction		
subjects affected / exposed	2 / 465 (0.43%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Intentional overdose		
subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Ligament rupture		
subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Meniscus injury		
subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Tibia fracture		
subjects affected / exposed	0 / 465 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Ulna fracture		

subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		

Ankle fracture

subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		

Multiple injuries

subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		

Post-traumatic pain

subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)		
occurrences causally related to treatment / all	0 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		

Nervous system disorders

Cerebellar ischaemia

subjects affected / exposed	0 / 465 (0.00%)	1 / 462 (0.22%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		

Cervicobrachial syndrome

subjects affected / exposed	0 / 465 (0.00%)	1 / 462 (0.22%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		

Dizziness

subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		

Hemiplegic migraine

subjects affected / exposed	0 / 465 (0.00%)	1 / 462 (0.22%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		

Hypoaesthesia

	subjects affected / exposed	0 / 465 (0.00%)	1 / 462 (0.22%)		
	occurrences causally related to treatment / all	0 / 0	0 / 1		
	deaths causally related to treatment / all	0 / 0	0 / 0		
Lumbosacral radiculopathy					
	subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (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 / 465 (0.22%)	4 / 462 (0.87%)		
	occurrences causally related to treatment / all	0 / 1	0 / 5		
	deaths causally related to treatment / all	0 / 0	0 / 0		
Paraesthesia					
	subjects affected / exposed	0 / 465 (0.00%)	1 / 462 (0.22%)		
	occurrences causally related to treatment / all	0 / 0	0 / 1		
	deaths causally related to treatment / all	0 / 0	0 / 0		
Syncope					
	subjects affected / exposed	0 / 465 (0.00%)	1 / 462 (0.22%)		
	occurrences causally related to treatment / all	0 / 0	0 / 1		
	deaths causally related to treatment / all	0 / 0	0 / 0		
Trigeminal neuralgia					
	subjects affected / exposed	0 / 465 (0.00%)	1 / 462 (0.22%)		
	occurrences causally related to treatment / all	0 / 0	0 / 1		
	deaths causally related to treatment / all	0 / 0	0 / 0		
Seizure					
	subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)		
	occurrences causally related to treatment / all	0 / 1	0 / 0		
	deaths causally related to treatment / all	0 / 0	0 / 0		
Blood and lymphatic system disorders					
Anaemia					
	subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)		
	occurrences causally related to treatment / all	0 / 1	0 / 0		
	deaths causally related to treatment / all	0 / 0	0 / 0		
Leukopenia					

subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness neurosensory			
subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	2 / 465 (0.43%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 465 (0.00%)	2 / 462 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 465 (0.00%)	1 / 462 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal polyp			
subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	0 / 465 (0.00%)	1 / 462 (0.22%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Obstructive pancreatitis				
subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Pancreatitis				
subjects affected / exposed	0 / 465 (0.00%)	1 / 462 (0.22%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Vomiting				
subjects affected / exposed	0 / 465 (0.00%)	1 / 462 (0.22%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Hepatobiliary disorders				
Biliary colic				
subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cholecystitis				
subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cholecystitis acute				
subjects affected / exposed	0 / 465 (0.00%)	1 / 462 (0.22%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cholecystitis chronic				
subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cholelithiasis migration				

subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (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

Nephrolithiasis

subjects affected / exposed	0 / 465 (0.00%)	2 / 462 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urinary retention

subjects affected / exposed	0 / 465 (0.00%)	1 / 462 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders

Back pain

subjects affected / exposed	2 / 465 (0.43%)	1 / 462 (0.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Femoroacetabular impingement

subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Intervertebral disc protrusion

subjects affected / exposed	0 / 465 (0.00%)	1 / 462 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Jaw cyst

subjects affected / exposed	0 / 465 (0.00%)	1 / 462 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Joint range of motion decreased

subjects affected / exposed	0 / 465 (0.00%)	1 / 462 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Morphoea			
subjects affected / exposed	0 / 465 (0.00%)	1 / 462 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle spasms			
subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial cyst			
subjects affected / exposed	0 / 465 (0.00%)	1 / 462 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovitis			
subjects affected / exposed	0 / 465 (0.00%)	1 / 462 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess sweat gland			
subjects affected / exposed	0 / 465 (0.00%)	1 / 462 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	3 / 465 (0.65%)	1 / 462 (0.22%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter infection			
subjects affected / exposed	0 / 465 (0.00%)	1 / 462 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			

subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (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	2 / 465 (0.43%)	0 / 462 (0.00%)		
occurrences causally related to treatment / all	0 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Influenza				
subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Kidney infection				
subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Neutropenic sepsis				
subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Osteomyelitis				
subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (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 / 465 (0.00%)	1 / 462 (0.22%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Pneumonia influenzal				
subjects affected / exposed	0 / 465 (0.00%)	1 / 462 (0.22%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Salpingo-oophoritis				

subjects affected / exposed	0 / 465 (0.00%)	1 / 462 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tick-borne viral encephalitis			
subjects affected / exposed	0 / 465 (0.00%)	1 / 462 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 465 (0.22%)	0 / 462 (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	1 / 465 (0.22%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 465 (0.00%)	1 / 462 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 465 (0.00%)	1 / 462 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	OMB 20mg	TER 14mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	282 / 465 (60.65%)	308 / 462 (66.67%)	
Investigations			
Blood immunoglobulin M decreased			
subjects affected / exposed	26 / 465 (5.59%)	13 / 462 (2.81%)	
occurrences (all)	51	22	
Injury, poisoning and procedural			

complications			
Injection related reaction			
subjects affected / exposed	74 / 465 (15.91%)	77 / 462 (16.67%)	
occurrences (all)	200	176	
Vascular disorders			
Hypertension			
subjects affected / exposed	15 / 465 (3.23%)	24 / 462 (5.19%)	
occurrences (all)	15	26	
Nervous system disorders			
Headache			
subjects affected / exposed	59 / 465 (12.69%)	53 / 462 (11.47%)	
occurrences (all)	77	78	
Paraesthesia			
subjects affected / exposed	17 / 465 (3.66%)	30 / 462 (6.49%)	
occurrences (all)	19	40	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	46 / 465 (9.89%)	39 / 462 (8.44%)	
occurrences (all)	52	42	
Injection site reaction			
subjects affected / exposed	41 / 465 (8.82%)	26 / 462 (5.63%)	
occurrences (all)	109	39	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	24 / 465 (5.16%)	64 / 462 (13.85%)	
occurrences (all)	25	89	
Nausea			
subjects affected / exposed	33 / 465 (7.10%)	33 / 462 (7.14%)	
occurrences (all)	34	40	
Abdominal pain			
subjects affected / exposed	23 / 465 (4.95%)	24 / 462 (5.19%)	
occurrences (all)	23	29	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	27 / 465 (5.81%)	65 / 462 (14.07%)	
occurrences (all)	28	66	
Psychiatric disorders			

Depression			
subjects affected / exposed	20 / 465 (4.30%)	26 / 462 (5.63%)	
occurrences (all)	21	26	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	30 / 465 (6.45%)	31 / 462 (6.71%)	
occurrences (all)	35	36	
Back pain			
subjects affected / exposed	35 / 465 (7.53%)	34 / 462 (7.36%)	
occurrences (all)	45	36	
Pain in extremity			
subjects affected / exposed	23 / 465 (4.95%)	36 / 462 (7.79%)	
occurrences (all)	23	39	
Infections and infestations			
Influenza			
subjects affected / exposed	31 / 465 (6.67%)	28 / 462 (6.06%)	
occurrences (all)	35	33	
Nasopharyngitis			
subjects affected / exposed	82 / 465 (17.63%)	69 / 462 (14.94%)	
occurrences (all)	136	109	
Upper respiratory tract infection			
subjects affected / exposed	47 / 465 (10.11%)	73 / 462 (15.80%)	
occurrences (all)	65	108	
Urinary tract infection			
subjects affected / exposed	41 / 465 (8.82%)	41 / 462 (8.87%)	
occurrences (all)	71	68	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol?   No

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 COMB157G2302 to address these endpoints.

Notes: