Clinical trial results:
Phase III: UbLiTuximab in Multiple Sclerosis Treatment Effects (ULTIMATE II STUDY)

Summary

EudraCT number	2017-000639-15
Trial protocol	GB PL ES HR
Global end of trial date	12 November 2020

Results information

Result version number	v1 (current)
This version publication date	27 November 2021
First version publication date	27 November 2021

Trial information

Trial identification

Sponsor protocol code	TG1101-RMS302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03277248
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	TG Therapeutics, Inc.
Sponsor organisation address	2 Gansevoort St; 9th Floor, New York, United States, 10014
Public contact	Clinical Support Team, TG Therapeutics, 1 877-575-8489, clinicalsupport@tgtxinc.com
Scientific contact	Clinical Support Team, TG Therapeutics, 1 877-575-8489, clinicalsupport@tgtxinc.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	12 November 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study determines the Annualized Relapse Rate (ARR) in subjects with RMS after 96 weeks (approximately 2 years) treatment with intravenous (IV) infusion of ublituximab/oral placebo compared to 14 mg oral teriflunomide/IV placebo.

Protection of trial subjects:

This study was conducted in accordance with the protocol and consensus ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all ICH GCP Guidelines. The Investigator or his/her representative explained the nature of the study to the subject or his/her legally authorized representative and answered all questions regarding the study. Subjects and/or their legally authorized representative were informed that their participation was voluntary. Subjects or their legally authorized representative were required to sign a statement of informed consent that met the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center. Investigative sites were instructed to obtain written informed consent before the subject was enrolled in the study and document the date the written consent was obtained. The authorized person obtaining the informed consent was also instructed to sign the ICF. Subjects were re-consented to the most current version of the ICF(s) during their participation and/or upon either IRAP-confirmed relapse or Treating Neurologist medically confirmed relapse. The DSMB was an independent group of individuals not involved in the study or study sites or had other conflicts of interest with the study and were charged with reviewing safety data and conduct of the trial. The committee met periodically, but at least annually to fulfill the duties and obligations outlined in the DSMB Charter. The committee received unblinded safety data to allow review and assessment by treatment group. In addition, the committee received unblinded efficacy data to perform a benefit/risk assessment. Based on their reviews and analyses of safety and efficacy data, the committee had the right to advise the Sponsor to stop the study after any meeting for efficacy or detrimental effects or futility.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	25 August 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	5 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Belarus: 64
Country: Number of subjects enrolled	Croatia: 49
Country: Number of subjects enrolled	Poland: 77

Country: Number of subjects enrolled	Russian Federation: 163
Country: Number of subjects enrolled	Ukraine: 143
Country: Number of subjects enrolled	United States: 36
Worldwide total number of subjects	545
EEA total number of subjects	134

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)	545
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 545 subjects were enrolled across investigative sites in Belarus, Spain, the United Kingdom, Croatia, Poland, Russia, Ukraine, and the United States from 25 August 2017 to 12 November 2020.

Pre-assignment

Screening details:

A total of 629 subjects were screened and of those, 545 were enrolled and randomized to receive either ublituximab/oral placebo or teriflunomide/IV placebo. In below reasons for not completed, Alt Treatment=Alternative Treatment.

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	Ublituximab + Oral Placebo

Arm description:

Subjects received ublituximab IV infusion, 150 milligrams (mg) over 4 hours (h) on Day 1 followed by 450 mg over 1 h on Days 15, 168, 336 and 504 (Week 72) along with the oral placebo tablet, once daily (QD) from Day 1 up to the last day of Week 95.

Arm type	Experimental
Investigational medicinal product name	Ublituximab
Investigational medicinal product code	TG-1101
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ublituximab 150 mg, 450 mg administered IV.

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

Dosage and administration details:

Placebo administered orally.

Arm title	Teriflunomide + IV Placebo

Arm description:

Subjects received teriflunomide 14 mg tablet, orally, QD from Day 1 up to the last day of Week 95 along with the placebo IV infusion on Days 1, 15, 168, 336 and 504 (Week 72).

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

Dosage and administration details: Teriflunomide 14 mg tablets administered orally.	
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: Placebo administered IV.	

Number of subjects in period 1	Ublituximab + Oral Placebo	Teriflunomide + IV Placebo
Started	272	273
Completed	254	239
Not completed	18	34
Adverse Event	3	1
Pregnancy	4	1
Alt Treatment/COVID-19 related/Unspecified Reasons	3	3
Investigator / sponsor decision	2	2
Lost to follow-up	-	2
Subject withdrawal of consent	6	23
Lack of efficacy	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Ublituximab + Oral Placebo
Reporting group description:	
Subjects received ublituximab IV infusion, 150 milligrams (mg) over 4 hours (h) on Day 1 followed by 450 mg over 1 h on Days 15, 168, 336 and 504 (Week 72) along with the oral placebo tablet, once daily (QD) from Day 1 up to the last day of Week 95.	
Reporting group title	Teriflunomide + IV Placebo
Reporting group description:	
Subjects received teriflunomide 14 mg tablet, orally, QD from Day 1 up to the last day of Week 95 along with the placebo IV infusion on Days 1, 15, 168, 336 and 504 (Week 72).	

Reporting group values	Ublituximab + Oral Placebo	Teriflunomide + IV Placebo	Total
Number of subjects	272	273	545
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	34.5	36.2	
standard deviation	± 8.76	± 8.97	-
Gender categorical Units: Subjects			
Female	178	176	354
Male	94	97	191
Race Units: Subjects			
Black or African American	2	3	5
White	269	269	538
Other	1	1	2
Ethnicity Units: Subjects			
Hispanic or Latino	6	3	9
Not Hispanic or Latino	262	263	525
Not Reported	2	2	4
Unknown	2	5	7

End points

End points reporting groups

Reporting group title	Ublituximab + Oral Placebo
Reporting group description:	
Subjects received ublituximab IV infusion, 150 milligrams (mg) over 4 hours (h) on Day 1 followed by 450 mg over 1 h on Days 15, 168, 336 and 504 (Week 72) along with the oral placebo tablet, once daily (QD) from Day 1 up to the last day of Week 95.	
Reporting group title	Teriflunomide + IV Placebo
Reporting group description:	
Subjects received teriflunomide 14 mg tablet, orally, QD from Day 1 up to the last day of Week 95 along with the placebo IV infusion on Days 1, 15, 168, 336 and 504 (Week 72).	

Primary: Annualized Relapse Rate (ARR)

End point title	Annualized Relapse Rate (ARR)
End point description:	
ARR is defined as the number of Independent Relapse Adjudication Committee (IRAP)-confirmed relapses per subject year. The estimate of ARR for a treatment group is the total number of relapses for subjects in the respective treatment group divided by the sum of treatment duration for subjects in that specific treatment group. Modified Intention-to-Treat (mITT) population consisted of all subjects in the ITT population who received at least one dose of study medication and had at least one baseline and post baseline efficacy assessment.	
End point type	Primary
End point timeframe:	
Up to 96 weeks	

End point values	Ublituximab + Oral Placebo	Teriflunomide + IV Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272	272		
Units: relapses per subject-years				
least squares mean (confidence interval 95%)	0.091 (0.049 to 0.169)	0.178 (0.109 to 0.291)		

Statistical analyses

Statistical analysis title	Annualized Relapse Rate (ARR)
Comparison groups	Ublituximab + Oral Placebo v Teriflunomide + IV Placebo
Number of subjects included in analysis	544
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0022 [1]
Method	Negative Binomial Model
Parameter estimate	Rate Ratio (Ublituximab / Teriflunomide)
Point estimate	0.509

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	0.784

Notes:

[1] - GEE (Generalized Estimating Equation) model for the relapse count per subject with logarithmic link function, treatment, region, and baseline Expanded Disability Status Scale (EDSS) strata as covariates and log (years of treatment) as offset.

Secondary: Total Number of Gadolinium (Gd)-Enhancing T1-Lesions Per Magnetic Resonance Imaging (MRI) Scan Per Subject

End point title	Total Number of Gadolinium (Gd)-Enhancing T1-Lesions Per Magnetic Resonance Imaging (MRI) Scan Per Subject

End point description:

The total number of Gd-enhancing T1-lesions were calculated as the sum of the individual number of lesions at Weeks 12, 24, 48, and 96, divided by the total number of MRI scans of the brain. mITT-MRI population consisted of subjects in the mITT population who had a baseline and at least 1 post-baseline MRI efficacy assessments.

End point type	Secondary

End point timeframe:

Weeks 12, 24, 48, and 96

End point values	Ublituximab + Oral Placebo	Teriflunomide + IV Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272	267		
Units: lesions per scan per subject				
least squares mean (confidence interval 95%)	0.009 (0.004 to 0.017)	0.250 (0.162 to 0.385)		

Statistical analyses

Statistical analysis title	Total Number of Gd-Enhancing T1-Lesions
Comparison groups	Ublituximab + Oral Placebo v Teriflunomide + IV Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Negative Binomial Model
Parameter estimate	Rate Ratio (Ublituximab / Teriflunomide)
Point estimate	0.035
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.019
upper limit	0.064

Notes:

[2] - GEE model for the relapse count per subject with logarithmic link function, treatment, region, and baseline EDSS strata as covariates and log (years of treatment) as offset.

Secondary: Total Number of New and Enlarging T2 Hyperintense Lesions (NELs) Per MRI Scan Per Subject

End point title	Total Number of New and Enlarging T2 Hyperintense Lesions (NELs) Per MRI Scan Per Subject

End point description:

The total number of NELs were calculated as the sum of the individual number of lesions at Weeks 24, 48, and 96, divided by the total number of MRI scans of the brain. mITT-MRI population consisted of subjects in the mITT population who had a baseline and at least 1 post-baseline MRI efficacy assessments. Overall number of subjects analysed signifies subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Weeks 24, 48, and 96

End point values	Ublituximab + Oral Placebo	Teriflunomide + IV Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	269	259		
Units: lesions per scan per subject				
least squares mean (confidence interval 95%)	0.282 (0.200 to 0.397)	2.831 (2.128 to 3.767)		

Statistical analyses

Statistical analysis title	Total Number of T2 NELs
Comparison groups	Ublituximab + Oral Placebo v Teriflunomide + IV Placebo
Number of subjects included in analysis	528
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Negative Binomial Model
Parameter estimate	Rate Ratio (Ublituximab / Teriflunomide)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.073
upper limit	0.136

Notes:

[3] - GEE model for the relapse count per subject with logarithmic link function, treatment, region, and baseline EDSS strata as covariates and log (years of treatment) as offset.

Secondary: Time to Confirmed Disability Progression (CDP) for at Least 12 Weeks

End point title	Time to Confirmed Disability Progression (CDP) for at Least 12 Weeks

End point description:

12-week CDP is defined as an increase in EDSS at least 1 point higher than the baseline EDSS if the baseline EDSS is ≤5.5 or at least 0.5 higher than baseline EDSS if the baseline EDSS is >5.5. EDSS is based on a standard neurological examination, (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, and cerebral) and ambulation function system assessments. EDSS disability scale ranges in 0.5-point steps from 0 (normal) to 10 (death) where higher scores indicate disability. Time to onset of 12-week CDP is time to progression to the EDSS change defined above. mITT population consisted of all subjects in ITT population who received at least one dose of study medication and had at least one baseline and post baseline efficacy assessment. As per protocol, data was summarized for mITT Population using pooled data from subjects in this study and TG1101-RMS301 [2017-000638-75].Due to EudraCT database constraints data cannot be entered here, please refer the table attachment.

End point type	Secondary

End point timeframe:

Up to Week 96

End point values	Ublituximab + Oral Placebo	Teriflunomide + IV Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: weeks				
median (inter-quartile range (Q1-Q3))	(to)	(to)		

Notes:

[4] - Data is not presented due to EudraCT database constraints.

[5] - Data is not presented due to EudraCT database constraints.

Attachments (see zip file)	Time to CDP for at Least 12 Weeks/t14-2-2-4-1-cdp12-a-mitt.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With No Evidence of Disease Activity (NEDA)

End point title	Percentage of Subjects With No Evidence of Disease Activity (NEDA)

End point description:

A subject with NEDA is defined as a subject without relapses confirmed by the IRAP, without MRI activities (no T1 Gd+ lesions and no new/enlarging T2 lesions), and no 12-week CDP. Any evidence of disease activity from Week 24 to Week 96 was counted as not reaching NEDA. Any evidence of disease activity before Week 24 was not counted. mITT population consisted of all subjects in the ITT population who received at least one dose of study medication and had at least one baseline and post baseline efficacy assessment.

End point type	Secondary

End point timeframe:

From Week 24 to Week 96

End point values	Ublituximab + Oral Placebo	Teriflunomide + IV Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272	272		
Units: percentage of subjects				
number (not applicable)	43.0	11.4		

Statistical analyses

Statistical analysis title	Percentage of Subjects with NEDA
Comparison groups	Ublituximab + Oral Placebo v Teriflunomide + IV Placebo
Number of subjects included in analysis	544
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Regression, Logistic
Parameter estimate	Odds Ratio (Ublituximab / Teriflunomide)
Point estimate	7.946
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.917
upper limit	12.841

Notes:

[6] - Logistic regression model with treatment, region, baseline EDSS strata and log transformed baseline MRI lesion counts (T1-unenhancing, T2, Gd-enhancing) as covariates.

Secondary: Percentage of Subjects With Impaired Symbol Digit Modalities Test (SDMT)

End point title	Percentage of Subjects With Impaired Symbol Digit Modalities Test (SDMT)

End point description:

The SDMT involves a simple substitution task using a reference key, the examinee has 90 seconds to pair specific numbers with given geometric figures. Responses are done verbally. The administration time is approximately 5 minutes. The total SDMT score for each visit ranging from 0-110 is defined as the total number of correct answers reported in the case report form (CRF), where high scores indicate better outcome. Impaired SDMT is defined as a decrease of at least 4 points from baseline at any post-baseline assessment up to the Week 96 visit. mITT population consisted of all subjects in the ITT population who received at least one dose of study medication and had at least one baseline and post baseline efficacy assessment.

End point type	Secondary

End point timeframe:

Baseline to Week 96

End point values	Ublituximab + Oral Placebo	Teriflunomide + IV Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272	272		
Units: percentage of subjects				
number (not applicable)	29.0	31.6		

Statistical analyses

Statistical analysis title	Percentage of Subjects with Impaired SDMT
Comparison groups	Ublituximab + Oral Placebo v Teriflunomide + IV Placebo
Number of subjects included in analysis	544
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.429 [7]
Method	Regression, Logistic
Parameter estimate	Odds Ratio (Ublituximab / Teriflunomide)
Point estimate	0.862
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.596
upper limit	1.246

Notes:

[7] - Logistic regression model with treatment, region, baseline EDSS strata and log transformed baseline MRI lesion counts (T1 unenhancing, T2, Gd enhancing) as covariates.

Secondary: Percent Change From Baseline in Brain Volume

End point title	Percent Change From Baseline in Brain Volume

End point description:

mITT-MRI population consisted of subjects in the mITT population who had a baseline and at least 1 post-baseline MRI efficacy assessments. Overall number of subjects analysed signifies subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 96

End point values	Ublituximab + Oral Placebo	Teriflunomide + IV Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	235	224		
Units: percent change				
least squares mean (confidence interval 95%)	-0.194 (-0.225 to -0.164)	-0.176 (-0.207 to -0.146)		

Statistical analyses

Statistical analysis title	Percent Change From Baseline in Brain Volume
Comparison groups	Ublituximab + Oral Placebo v Teriflunomide + IV Placebo
Number of subjects included in analysis	459
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3108 [8]
Method	Mixed Model Repeated Measures
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.018
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.053
upper limit	0.017

Notes:

[8] - MMRM model includes treatment, region, baseline EDSS strata, visit, treatment-by-visit interaction, and baseline volume (cube root transformed) as covariates and an unstructured covariance matrix.

Secondary: Percentage of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (TESAEs)

End point title	Percentage of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (TESAEs)

End point description:

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product. A serious AE is defined as any untoward medical occurrence that: results in death, is immediately life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, and/or causes a congenital anomaly/birth defect. TEAEs are AEs that start or worsen after receiving the study drug. Safety population included all subjects who received at least one dose of study drug (ublituximab or teriflunomide, with corresponding placebos).

End point type	Secondary

End point timeframe:

From the first dose of study drug through the end of the study (up to approximately 116 weeks)

End point values	Ublituximab + Oral Placebo	Teriflunomide + IV Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272	273		
Units: percentage of subjects				
number (not applicable)				
TEAEs	92.3	93.8		
TESAEs	10.3	7.7		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug through the end of the study (up to approximately 116 weeks)

Adverse event reporting additional description:

Safety population included all subjects who received at least one dose of study drug (ublituximab or teriflunomide, with corresponding placebos).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Ublituximab + Oral Placebo

Reporting group description:

Subjects received ublituximab IV infusion, 150 milligrams (mg) over 4 hours (h) on Day 1 followed by 450 mg over 1 h on Days 15, 168, 336 and 504 (Week 72) along with the oral placebo tablet, once daily (QD) from Day 1 up to the last day of Week 95.

Reporting group title	Teriflunomide + IV Placebo

Reporting group description:

Subjects received teriflunomide 14 mg tablet, orally, QD from Day 1 up to the last day of Week 95 along with the placebo IV infusion on Days 1, 15, 168, 336 and 504 (Week 72).

Serious adverse events	Ublituximab + Oral Placebo	Teriflunomide + IV Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 272 (10.29%)	21 / 273 (7.69%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Desmoid tumour			
subjects affected / exposed	1 / 272 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial stromal sarcoma			
subjects affected / exposed	1 / 272 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine cancer			

subjects affected / exposed	1 / 272 (0.37%)	0 / 273 (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 / 272 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 272 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Ovarian cystectomy			
subjects affected / exposed	1 / 272 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pituitary gland operation			
subjects affected / exposed	1 / 272 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Decreased activity			
subjects affected / exposed	1 / 272 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 272 (0.37%)	0 / 273 (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	1 / 272 (0.37%)	0 / 273 (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			
Ovarian cyst			
subjects affected / exposed	1 / 272 (0.37%)	0 / 273 (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			
Concussion			
subjects affected / exposed	0 / 272 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	0 / 272 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 272 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 272 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coordination abnormal			
subjects affected / exposed	1 / 272 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysaesthesia			
subjects affected / exposed	1 / 272 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			

subjects affected / exposed	0 / 272 (0.00%)	2 / 273 (0.73%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
subjects affected / exposed	0 / 272 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Bone marrow toxicity			
subjects affected / exposed	1 / 272 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 272 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Astigmatism			
subjects affected / exposed	0 / 272 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	0 / 272 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glaucoma			
subjects affected / exposed	1 / 272 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal degeneration			
subjects affected / exposed	0 / 272 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal hernia			
subjects affected / exposed	1 / 272 (0.37%)	0 / 273 (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 / 272 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis chronic			
subjects affected / exposed	0 / 272 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 272 (0.00%)	1 / 273 (0.37%)	
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			
Muscular weakness			
subjects affected / exposed	1 / 272 (0.37%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	3 / 272 (1.10%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 272 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			

subjects affected / exposed	0 / 272 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	2 / 272 (0.74%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic hepatitis B			
subjects affected / exposed	1 / 272 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic tonsillitis			
subjects affected / exposed	0 / 272 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complicated appendicitis			
subjects affected / exposed	1 / 272 (0.37%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymitis			
subjects affected / exposed	1 / 272 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	1 / 272 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periodontitis			
subjects affected / exposed	0 / 272 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			

subjects affected / exposed	0 / 272 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pilonidal cyst			
subjects affected / exposed	0 / 272 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 272 (0.74%)	2 / 273 (0.73%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 272 (0.00%)	2 / 273 (0.73%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis chronic			
subjects affected / exposed	0 / 272 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 272 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	0 / 272 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 272 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	1 / 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	Ublituximab + Oral Placebo	Teriflunomide + IV Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	234 / 272 (86.03%)	233 / 273 (85.35%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	10 / 272 (3.68%)	15 / 273 (5.49%)	
occurrences (all)	16	26	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	34 / 272 (12.50%)	14 / 273 (5.13%)	
occurrences (all)	46	19	
Influenza like illness			
subjects affected / exposed	28 / 272 (10.29%)	7 / 273 (2.56%)	
occurrences (all)	41	9	
Chills			
subjects affected / exposed	25 / 272 (9.19%)	3 / 273 (1.10%)	
occurrences (all)	30	3	
Hyperthermia			
subjects affected / exposed	18 / 272 (6.62%)	4 / 273 (1.47%)	
occurrences (all)	21	4	
Asthenia			
subjects affected / exposed	16 / 272 (5.88%)	20 / 273 (7.33%)	
occurrences (all)	18	25	
Fatigue			
subjects affected / exposed	15 / 272 (5.51%)	11 / 273 (4.03%)	
occurrences (all)	27	21	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	12 / 272 (4.41%)	15 / 273 (5.49%)	
occurrences (all)	43	49	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			

subjects affected / exposed	18 / 272 (6.62%)	9 / 273 (3.30%)	
occurrences (all)	27	11	
Throat irritation			
subjects affected / exposed	14 / 272 (5.15%)	1 / 273 (0.37%)	
occurrences (all)	24	2	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	21 / 272 (7.72%)	8 / 273 (2.93%)	
occurrences (all)	30	22	
Anxiety			
subjects affected / exposed	16 / 272 (5.88%)	12 / 273 (4.40%)	
occurrences (all)	24	14	
Investigations			
Lymphocyte count decreased			
subjects affected / exposed	15 / 272 (5.51%)	2 / 273 (0.73%)	
occurrences (all)	22	2	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	19 / 272 (6.99%)	2 / 273 (0.73%)	
occurrences (all)	23	4	
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	20 / 272 (7.35%)	5 / 273 (1.83%)	
occurrences (all)	20	6	
Nervous system disorders			
Headache			
subjects affected / exposed	103 / 272 (37.87%)	87 / 273 (31.87%)	
occurrences (all)	327	357	
Dizziness			
subjects affected / exposed	16 / 272 (5.88%)	12 / 273 (4.40%)	
occurrences (all)	22	17	
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	26 / 272 (9.56%)	2 / 273 (0.73%)	
occurrences (all)	32	3	
Anaemia			

subjects affected / exposed	9 / 272 (3.31%)	15 / 273 (5.49%)	
occurrences (all)	16	32	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	29 / 272 (10.66%)	28 / 273 (10.26%)	
occurrences (all)	43	32	
Abdominal pain			
subjects affected / exposed	28 / 272 (10.29%)	12 / 273 (4.40%)	
occurrences (all)	36	12	
Diarrhoea			
subjects affected / exposed	25 / 272 (9.19%)	32 / 273 (11.72%)	
occurrences (all)	39	39	
Constipation			
subjects affected / exposed	16 / 272 (5.88%)	17 / 273 (6.23%)	
occurrences (all)	19	17	
Dyspepsia			
subjects affected / exposed	16 / 272 (5.88%)	15 / 273 (5.49%)	
occurrences (all)	18	18	
Toothache			
subjects affected / exposed	16 / 272 (5.88%)	15 / 273 (5.49%)	
occurrences (all)	24	25	
Abdominal pain upper			
subjects affected / exposed	15 / 272 (5.51%)	9 / 273 (3.30%)	
occurrences (all)	22	15	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	13 / 272 (4.78%)	48 / 273 (17.58%)	
occurrences (all)	15	49	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	35 / 272 (12.87%)	23 / 273 (8.42%)	
occurrences (all)	47	38	
Arthralgia			
subjects affected / exposed	17 / 272 (6.25%)	13 / 273 (4.76%)	
occurrences (all)	22	21	
Pain in extremity			

subjects affected / exposed	16 / 272 (5.88%)	13 / 273 (4.76%)	
occurrences (all)	24	19	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	67 / 272 (24.63%)	54 / 273 (19.78%)	
occurrences (all)	147	108	
Respiratory tract infection			
subjects affected / exposed	30 / 272 (11.03%)	28 / 273 (10.26%)	
occurrences (all)	48	37	
Pharyngitis			
subjects affected / exposed	24 / 272 (8.82%)	6 / 273 (2.20%)	
occurrences (all)	34	8	
Upper respiratory tract infection			
subjects affected / exposed	24 / 272 (8.82%)	25 / 273 (9.16%)	
occurrences (all)	35	31	
Respiratory tract infection viral			
subjects affected / exposed	22 / 272 (8.09%)	23 / 273 (8.42%)	
occurrences (all)	42	30	
Cystitis			
subjects affected / exposed	17 / 272 (6.25%)	12 / 273 (4.40%)	
occurrences (all)	23	13	
Sinusitis			
subjects affected / exposed	17 / 272 (6.25%)	13 / 273 (4.76%)	
occurrences (all)	20	18	
Oral herpes			
subjects affected / exposed	14 / 272 (5.15%)	16 / 273 (5.86%)	
occurrences (all)	20	25	
Rhinitis			
subjects affected / exposed	9 / 272 (3.31%)	14 / 273 (5.13%)	
occurrences (all)	11	16	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 June 2017	• A sentence was added to include additional analysis of relapses from a more specific timeframe. The sentence reads as follows: "Relapses that occur after study drugs are withdrawn will be assessed over the remainder of the study period and this data will be utilized as part of additional sensitivity analysis (described in the statistical plan) as long as the subject has not withdrawn their consent to be in the trial." • The interface between IRAP and the study sites were updated to as follows: "IRAP adjudicates each case based on all available data provided for that case and members are not permitted to contact the site or the sponsor for additional information." • The change in EDSS score for defining progression of disability were updated to state as follows: "…if a subject experiences at least 1.0 point increase on the EDSS when a baseline score is < 5.5…" • The assessment tables now stipulated EDSS must be assessed 1 day prior to randomization. • Intent to treat definition was updated in the body of the protocol. • Now included is a hierarchy analysis, sensitivity analysis for secondary endpoints and subjects who withdraw from study. • The timeframe of relapse assessment was further defined. • Interim sample size reassessment for relapses was further defined. • Minor typographical errors
03 August 2017	• Included information regarding a new vial size for ublituximab. • Updated to reflect changes in adverse events as reported in the revised Investigator Brochure (Version 5.0; dated 01 August 2017). • Minor typographical errors
17 January 2020	• Clarification of the exclusion criteria to avoid potential misinterpretation. • Clarification regarding the active comparator to confirm bioequivalent teriflunomide product was used in the study. • Clarification on MRI and Pharmacokinetic (PK) windows. • Minor administrative revisions to remove inconsistencies. • Advised subjects to seek immediate medical help and inform the investigator if they experience signs or symptoms of an infection. • Provided information on TG1101-RMS303 which is the Open Label Extension of TG1101-RMS301 and TG1101-RMS302.
04 September 2020	•Updated Secondary Endpoints. •Updated Tertiary Endpoints. •Specified timing of teriflunomide elimination procedure post discontinuation from study treatment. •Added reference to pharmacists as site team members. •Defined Treating Neurologist Medically Confirmed relapses. • Added requirement to re-consent subjects upon Treating Neurologist medically confirmed relapse. • Added guidance to assessments during dosing delay due to lab abnormalities and suspected relapse Provided definition of Infusion Related Reaction and that they will be analyzed separately. • Listed and clarified all pooled analysis. • Further defined Treatment Emergent Adverse Events Replaced protocol list of Adverse Events of Special Interest with reference to valid Investigator Brochure (IB).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported