Clinical trial results:
Phase III: UbLiTuximab In Multiple Sclerosis Treatment Effects (ULTIMATE I STUDY)

Summary

EudraCT number	2017-000638-75
Trial protocol	GB PL ES
Global end of trial date	06 November 2020

Results information

Result version number	v1 (current)
This version publication date	19 November 2021
First version publication date	19 November 2021

Trial information

Trial identification

Sponsor protocol code	TG1101-RMS301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03277261
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	23 July 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 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 Relapsing Forms of Multiple Sclerosis (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	19 September 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	Russian Federation: 133
Country: Number of subjects enrolled	Serbia: 64

Country: Number of subjects enrolled	Ukraine: 107
Country: Number of subjects enrolled	Belarus: 64
Country: Number of subjects enrolled	Georgia: 83
Country: Number of subjects enrolled	United States: 48
Country: Number of subjects enrolled	Poland: 41
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	United Kingdom: 4
Worldwide total number of subjects	549
EEA total number of subjects	46

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)	549
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 549 subjects were enrolled across investigative sites in Belarus, Spain, the United Kingdom, Georgia, Poland, Russia, Serbia, Ukraine, and the United States from 19 September 2017 to 6 November 2020.

Pre-assignment

Screening details:

A total of 646 subjects were screened and of those, 549 were enrolled and randomized to receive either ublituximab/oral placebo or teriflunomide/IV placebo.

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Assessor, Subject

Blinding implementation details:

All oral study drugs were prepared in identical tablets and containers and all IV study drugs were prepared in identical vials to ensure adequate blinding. All personnel involved with the conduct and interpretation of the study, including the Investigators, study site personnel, and Sponsor were blinded to treatment until after the database was locked and the study was officially unblinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ublituximab + Oral Placebo

Arm description:

Subjects were administered ublituximab 150 milligrams (mg), intravenous (IV) infusion 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 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	
Other name	TG-1101
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 were administered 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 injection
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	274	275
Completed	240	252
Not completed	34	23
Consent withdrawn by subject	6	15
Investigator / Sponsor decision	4	2
Pregnancy	2	-
Adverse event	17	1
Other-Alternative Treatment/Unspecified Reasons	1	1
Lost to follow-up	2	2
Lack of efficacy	2	2

Baseline characteristics

Reporting groups	
Reporting group title	Ublituximab + Oral Placebo
Reporting group description:	
Subjects were administered ublituximab 150 milligrams (mg), intravenous (IV) infusion 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 once daily (QD) from Day 1 up to the last day of Week 95.	
Reporting group title	Teriflunomide + IV Placebo
Reporting group description:	
Subjects were administered 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	274	275	549
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	36.3	37.0	
standard deviation	± 8.48	± 9.62	-
Gender categorical Units: Subjects			
Female	167	180	347
Male	107	95	202
Ethnicity Units: Subjects			
Hispanic or Latino	7	2	9
Not Hispanic or Latino	263	267	530
Unknown or Not Reported	4	6	10
Race/Ethnicity Units: Subjects			
Black or African American	6	6	12
White	267	267	534
Native Hawaiian or Other Pacific Islander	1	0	1
Other	0	2	2

End points

End points reporting groups

Reporting group title	Ublituximab + Oral Placebo

Reporting group description:

Subjects were administered ublituximab 150 milligrams (mg), intravenous (IV) infusion 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 once daily (QD) from Day 1 up to the last day of Week 95.

Reporting group title	Teriflunomide + IV Placebo

Reporting group description:

Subjects were administered 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).

Subject analysis set title	Ublituximab + Oral Placebo
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Subjects were administered ublituximab 150 mg, IV infusion over 4 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 QD from Day 1 up to the last day of Week 95. As per protocol, data was summarized for the mITT Population using pooled data from subjects in this study and TG1101-RMS302 [NCT03277248].

Subject analysis set title	Teriflunomide + IV Placebo
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Subjects were administered 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). As per protocol, data was summarized for the mITT Population using pooled data from subjects in this study and TG1101-RMS302 [NCT03277248].

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 Panel (IRAP)-confirmed relapses per subject year. The estimate of ARR for a treatment group is the total number of relapses for subject in the respective treatment group divided by the sum of treatment duration for subject 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 have 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	271	274		
Units: relapses per subject-years				
least squares mean (confidence interval 95%)	0.076 (0.042 to 0.138)	0.188 (0.124 to 0.283)		

Statistical analyses

Statistical analysis title	Annualized Relapse Rate (ARR)
Comparison groups	Teriflunomide + IV Placebo v Ublituximab + Oral Placebo
Number of subjects included in analysis	545
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Negative Binomial Model
Parameter estimate	Rate Ratio (Ublituximab/Teriflunomide)
Point estimate	0.406
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.268
upper limit	0.615

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 included subjects in mITT population who have baseline and post-baseline MRI efficacy assessments. Overall number of subjects analyzed signifies subjects who were evaluable for this endpoint.

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	264	269		
Units: lesions per scan per subject				
least squares mean (confidence interval 95%)	0.016 (0.008 to 0.032)	0.491 (0.355 to 0.679)		

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	533
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Negative Binomial Model
Parameter estimate	Rate Ratio (Ublituximab/Teriflunomide)
Point estimate	0.033
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.019
upper limit	0.058

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 included subjects in mITT population who have baseline and post-baseline MRI efficacy assessments. Overall number of subjects analyzed 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	260	267		
Units: lesions per scan per subject				
least squares mean (confidence interval 95%)	0.213 (0.144 to 0.316)	2.789 (2.136 to 3.643)		

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	527
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Negative Binomial Model
Parameter estimate	Rate Ratio (Ublituximab/Teriflunomide)
Point estimate	0.076

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.056
upper limit	0.104

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 baseline EDSS if the baseline EDSS is ≤5.5 or at least 0.5 higher than the 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. The time to onset of 12-week CDP is the time to progression to the EDSS change defined above. mITT population = all subjects in the ITT population who received at least one dose of study drug and have 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-RMS302 [2017-000639-15]. 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	Subject analysis set	Subject analysis set		
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 have at least one baseline and post baseline efficacy assessment.

End point type	Secondary

End point timeframe:

Week 24 up to Week 96

End point values	Ublituximab + Oral Placebo	Teriflunomide + IV Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	271	274		
Units: percentage of subjects				
number (not applicable)	44.6	15.0		

Statistical analyses

Statistical analysis title	Percentage of Subjects with NEDA
Comparison groups	Teriflunomide + IV Placebo v Ublituximab + Oral Placebo
Number of subjects included in analysis	545
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Regression, Logistic
Parameter estimate	Odds Ratio (Ublituximab/Teriflunomide)
Point estimate	5.442
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.536
upper limit	8.375

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 from baseline of at least 4 points 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 have at least one baseline and post baseline efficacy assessment.

End point type	Secondary

End point timeframe:

Baseline up to Week 96

End point values	Ublituximab + Oral Placebo	Teriflunomide + IV Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	271	274		
Units: percentage of subjects				
number (not applicable)	29.2	31.8		

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	545
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4669 [7]
Method	Regression, Logistic
Parameter estimate	Odds Ratio (Ublituximab/Teriflunomide)
Point estimate	0.872
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.603
upper limit	1.261

Notes:

[7] - Logistic regression model with treatment, region, baseline EDSS strata, and log-transformed baseline MRI 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 included subjects in mITT population who have baseline and post-baseline MRI efficacy assessments. Overall number of subjects analyzed signifies subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to Week 96

End point values	Ublituximab + Oral Placebo	Teriflunomide + IV Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204	207		
Units: percent change				
least squares mean (confidence interval 95%)	-0.197 (-0.228 to -0.166)	-0.125 (-0.155 to -0.095)		

Statistical analyses

Statistical analysis title	Percent Change From Baseline in Brain Volume
Comparison groups	Teriflunomide + IV Placebo v Ublituximab + Oral Placebo
Number of subjects included in analysis	411
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	Mixed Model Repeated Measure (MMRM)
Parameter estimate	Least squares mean difference
Point estimate	-0.072
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.107
upper limit	-0.036

Notes:

[8] - The 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. A TEAE is an AE that starts or worsens after receiving 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	273	275		
Units: percentage of subjects				
number (not applicable)				
TEAEs	86.1	89.1		
TESAEs	11.4	6.9		

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:

All-Cause Mortality: All the enrolled subjects (i.e subjects exposed n=274, 275); Adverse Events: 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 were administered ublituximab 150 milligrams (mg), intravenous (IV) infusion 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 once daily (QD) from Day 1 up to the last day of Week 95.

Reporting group title	Teriflunomide + IV Placebo

Reporting group description:

Subjects were administered 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	31 / 273 (11.36%)	19 / 275 (6.91%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Varicose vein			
subjects affected / exposed	1 / 273 (0.37%)	0 / 275 (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			
Medical device removal			
subjects affected / exposed	1 / 273 (0.37%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Ectopic pregnancy			

subjects affected / exposed	1 / 273 (0.37%)	0 / 275 (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			
Asthenia			
subjects affected / exposed	0 / 273 (0.00%)	1 / 275 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 273 (0.37%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	1 / 273 (0.37%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian cyst ruptured			
subjects affected / exposed	0 / 273 (0.00%)	1 / 275 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine haemorrhage			
subjects affected / exposed	0 / 273 (0.00%)	1 / 275 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Affective disorder			
subjects affected / exposed	1 / 273 (0.37%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental disorder			

subjects affected / exposed	1 / 273 (0.37%)	0 / 275 (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	0 / 273 (0.00%)	1 / 275 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Lymphocyte count decreased			
subjects affected / exposed	1 / 273 (0.37%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	1 / 273 (0.37%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 273 (0.37%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	1 / 273 (0.37%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	1 / 273 (0.37%)	0 / 275 (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			
Acoustic neuritis			
subjects affected / exposed	0 / 273 (0.00%)	1 / 275 (0.36%)	
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 / 273 (0.37%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological symptom			
subjects affected / exposed	1 / 273 (0.37%)	4 / 275 (1.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 273 (0.37%)	0 / 275 (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			
Neutropenia			
subjects affected / exposed	1 / 273 (0.37%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Oesophageal achalasia			
subjects affected / exposed	0 / 273 (0.00%)	1 / 275 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis chronic			
subjects affected / exposed	1 / 273 (0.37%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 273 (0.00%)	1 / 275 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rosacea			

subjects affected / exposed	0 / 273 (0.00%)	1 / 275 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Tubulointerstitial nephritis			
subjects affected / exposed	1 / 273 (0.37%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 273 (0.00%)	1 / 275 (0.36%)	
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	0 / 273 (0.00%)	1 / 275 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc disorder			
subjects affected / exposed	0 / 273 (0.00%)	1 / 275 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 273 (0.00%)	1 / 275 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 273 (0.37%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 273 (0.37%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 273 (0.37%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	0 / 273 (0.00%)	1 / 275 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bullous erysipelas			
subjects affected / exposed	1 / 273 (0.37%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	2 / 273 (0.73%)	1 / 275 (0.36%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system enteroviral infection			
subjects affected / exposed	2 / 273 (0.73%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	1 / 273 (0.37%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lyme disease			
subjects affected / exposed	0 / 273 (0.00%)	1 / 275 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Measles			
subjects affected / exposed	1 / 273 (0.37%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Meningoencephalitis viral			
subjects affected / exposed	1 / 273 (0.37%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillar abscess			
subjects affected / exposed	1 / 273 (0.37%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 273 (1.10%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	1 / 273 (0.37%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 273 (0.00%)	1 / 275 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salpingitis			
subjects affected / exposed	1 / 273 (0.37%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 273 (0.37%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 273 (0.00%)	2 / 275 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
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	197 / 273 (72.16%)	181 / 275 (65.82%)	
Investigations			
Lymphocyte count decreased			
subjects affected / exposed	33 / 273 (12.09%)	8 / 275 (2.91%)	
occurrences (all)	33	8	
Aspartate aminotransferase increased			
subjects affected / exposed	14 / 273 (5.13%)	4 / 275 (1.45%)	
occurrences (all)	23	4	
Alanine aminotransferase increased			
subjects affected / exposed	12 / 273 (4.40%)	16 / 275 (5.82%)	
occurrences (all)	17	26	
Vascular disorders			
Hypertension			
subjects affected / exposed	12 / 273 (4.40%)	23 / 275 (8.36%)	
occurrences (all)	18	33	
Nervous system disorders			
Headache			
subjects affected / exposed	84 / 273 (30.77%)	59 / 275 (21.45%)	
occurrences (all)	254	189	
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	27 / 273 (9.89%)	4 / 275 (1.45%)	
occurrences (all)	28	5	
Neutropenia			
subjects affected / exposed	11 / 273 (4.03%)	15 / 275 (5.45%)	
occurrences (all)	14	22	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	41 / 273 (15.02%)	13 / 275 (4.73%)	
occurrences (all)	46	18	
Chills			

subjects affected / exposed	19 / 273 (6.96%)	1 / 275 (0.36%)	
occurrences (all)	20	1	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	29 / 273 (10.62%)	15 / 275 (5.45%)	
occurrences (all)	43	22	
Diarrhoea			
subjects affected / exposed	19 / 273 (6.96%)	26 / 275 (9.45%)	
occurrences (all)	43	33	
Abdominal pain			
subjects affected / exposed	15 / 273 (5.49%)	9 / 275 (3.27%)	
occurrences (all)	21	17	
Abdominal pain upper			
subjects affected / exposed	7 / 273 (2.56%)	14 / 275 (5.09%)	
occurrences (all)	12	21	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	6 / 273 (2.20%)	36 / 275 (13.09%)	
occurrences (all)	8	40	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	16 / 273 (5.86%)	30 / 275 (10.91%)	
occurrences (all)	19	41	
Pain in extremity			
subjects affected / exposed	15 / 273 (5.49%)	12 / 275 (4.36%)	
occurrences (all)	22	19	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	34 / 273 (12.45%)	44 / 275 (16.00%)	
occurrences (all)	59	82	
Respiratory tract infection viral			
subjects affected / exposed	20 / 273 (7.33%)	8 / 275 (2.91%)	
occurrences (all)	36	12	
Rhinitis			
subjects affected / exposed	18 / 273 (6.59%)	8 / 275 (2.91%)	
occurrences (all)	23	9	

Upper respiratory tract infection subjects affected / exposed occurrences (all)	16 / 273 (5.86%) 16	15 / 275 (5.45%) 22	
Urinary tract infection subjects affected / exposed occurrences (all)	11 / 273 (4.03%) 24	16 / 275 (5.82%) 25	

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 stipulated as EDSS must be assessed 1 day prior to randomization. • Intent to treat definition was updated in the body of the protocol. • Now included 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 sections to reflect changes in adverse events as reported in the revised Investigator Brochure. • 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 is used in the study. • Clarification on MRI and Pharmacokinetic (PK) windows. • Minor administrative revisions to remove inconsistencies. • Advise for 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 was 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 IB.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported