Clinical trial results:
A 24-week phase IIb, randomized, double-blind, placebo-controlled, multicenter study to investigate the efficacy and safety of tregalizumab (BT061) in combination with methotrexate in the treatment of subjects with active rheumatoid arthritis who have had an inadequate response to methotrexate alone, followed by a 24-week extension phase:
T cell REgulating Arthritis Trial 2b (TREAT 2b)

Summary

EudraCT number	2013-000114-38
Trial protocol	DE HU CZ EE LT SK BG
Global end of trial date	31 July 2015

Results information

Result version number	v1 (current)
This version publication date	30 October 2021
First version publication date	30 October 2021
Summary attachment (see zip file)	Biotest-BT061 (Study986_final_CSR_Synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	Study 986

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01999192
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biotest AG
Sponsor organisation address	Landsteiner Str. 5, Dreieich , Germany, 63303
Public contact	Clinical Trial Information, Biotest AG, +49 (0)8011225, 986@biotest.de
Scientific contact	Clinical Trial Information, Biotest AG, +49 (0)8011225, 986@biotest.de

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	31 July 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 July 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy and safety of three doses of tregalizumab administered over 24 weeks, followed by a 24-week extension phase (active treatment only),
in combination with methotrexate (MTX), for the treatment of adult subjects with active rheumatoid arthritis (RA) who have had an inadequate response to MTX alone
(MTX-IR).

Protection of trial subjects:

1) Possibility of home administration after training at site to reduce visit burden
2) 'Rescue' pain/analgesic treatment on demand
3) Physical exam and test of laboratory safety parameters at each visit
4) Special withdrawal criteria:
   (a) CD4 cell count below 400/µL measured at two sequential assessments 2 weeks apart
   (b) Any opportunistic or systemic infection requiring parenteral anti-infectives or hospitalization
   (c) Active TB
5) Collection of AEs that occurred during the injection or since their last visit
6) Regular medical review of subject data

Background therapy:

Methotrexate ≥15 mg (or ≥12.5 mg in case of MTX intolerance)

Evidence for comparator: -

Actual start date of recruitment	20 September 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Mexico: 32
Country: Number of subjects enrolled	United States: 11
Country: Number of subjects enrolled	Russian Federation: 53
Country: Number of subjects enrolled	Ukraine: 38
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Serbia: 9
Country: Number of subjects enrolled	Poland: 67
Country: Number of subjects enrolled	Slovakia: 7
Country: Number of subjects enrolled	Bulgaria: 30
Country: Number of subjects enrolled	Czech Republic: 30
Country: Number of subjects enrolled	Estonia: 5

Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Hungary: 18
Country: Number of subjects enrolled	Lithuania: 5
Worldwide total number of subjects	321
EEA total number of subjects	176

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)	281
From 65 to 84 years	40
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In total, 321 subjects were randomized (83, 80, and 78 in the BT061 25 mg, 100 mg and 200 mg groups, respectively and 80 in the placebo group). A total of 321 subjects were included in the Safety set (SS), 313 were included in the Full analysis set (FAS), and 183 subjects were included in the Per-protocol set (PPS).

Pre-assignment

Screening details:

screening period (28-OCT-2013 to 30-Sep-2014): 715 patients screened and 321 patients randmised;
Main inclusion: subjects 18-75 yrs with active RA ≥6 months; stable MTX treatment for ≥12 weeks; ≥6 swollen/tender joints at 28-joint count;
Exclusion: Anti-TNF failures; Previous exposure to systemic biologics.

Period 1

Period 1 title	Main Phase 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

double dummy techniques; BT061 solution and the placebo formulation with identical volume and in identical containers.
Systemic effects of BT061 on laboratory parameters : lymphocytes and CD3CD4 cell count and IL-6, TNF-α levels, and CRP were kept blinded during the study.
Unblinding was only to be carried out if a medical emergency required the identification of the IMP for that particular subject. Any subject for whom the blind was broken was to be discontinued from the study.

Arms

Are arms mutually exclusive?	No
Arm title	Placebo

Arm description:

Placebo SC, once weekly

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

Dosage and administration details:

1 ml SC once weekly

Arm title	Tregalizumab 25 mg

Arm description:

Active treatment : Tregalizumab 25 mg SC, once weekly

Arm type	Experimental
Investigational medicinal product name	Tregalizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

25 mg SC once weekly

Arm title	Tregalizumab 100 mg
Arm description: Active treatment: Tregalizumab 100 mg SC, once weekly	
Arm type	Experimental
Investigational medicinal product name	Tregalizumab 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details: 100 mg SC once weekly	

Arm title	Tregalizumab 200 mg
Arm description: Active treatment: Tregalizumab 200 mg SC, once weekly	
Arm type	Experimental
Investigational medicinal product name	Tregalizumab 200 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details: 200 mg SC once weekly	

Number of subjects in period 1	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg
Started	80	83	80
Qualify for FAS	79	80	78
Completed	72	72	70
Not completed	8	11	10
Adverse event, serious fatal	-	-	-
Consent withdrawn by subject	3	2	3
Adverse event, non-fatal	2	5	2
Failure to meet randomisation criteria	2	2	2
NK	1	-	1
Lost to follow-up	-	1	-
Lack of efficacy	-	1	2

Number of subjects in period 1	Tregalizumab 200 mg
Started	78
Qualify for FAS	76
Completed	70
Not completed	8
Adverse event, serious fatal	1
Consent withdrawn by subject	4

Adverse event, non-fatal	1
Failure to meet randomisation criteria	1
NK	1
Lost to follow-up	-
Lack of efficacy	-

Period 2

Period 2 title	Main Phase 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:
same as Main Phase 1

Arms

Are arms mutually exclusive?	No
Arm title	Placebo

Arm description:
no active component

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

Dosage and administration details:
1 ml SC once weekly

Arm title	Tregalizumab 25 mg

Arm description:
Active treatment

Arm type	Experimental
Investigational medicinal product name	Tregalizumab 25mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:
25 mg SC once weekly

Arm title	Tregalizumab 100 mg

Arm description:
Active treatment

Arm type	Experimental

Investigational medicinal product name	Tregalizumab 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:
100 mg SC once weekly

Arm title	Tregalizumab 200 mg

Arm description:
Active treatment

Arm type	Experimental
Investigational medicinal product name	Tregalizumab 200 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:
200 mg SC once weekly

Number of subjects in period 2	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg
Started	44	53	49
Completed	43	46	44
Not completed	1	7	5
Consent withdrawn by subject	-	2	1
Adverse event, non-fatal	1	2	-
Failure to meet randomisation criteria	-	1	3
NK	-	2	-
Lack of efficacy	-	-	1

Number of subjects in period 2	Tregalizumab 200 mg
Started	69
Completed	56
Not completed	13
Consent withdrawn by subject	3
Adverse event, non-fatal	5
Failure to meet randomisation criteria	3
NK	-
Lack of efficacy	2

Period 3

Period 3 title	Extension Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	No
Arm title	Tregalizumab 25 mg

Arm description:
Active treatment

Arm type	Experimental
Investigational medicinal product name	Tregalizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:
25 mg SC once weekly

Arm title	Tregalizumab 100 mg

Arm description:
Active treatment

Arm type	Experimental
Investigational medicinal product name	Tregalizumab 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:
100 mg SC once weekly

Arm title	Tregalizumab 200 mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Tregalizumab 200 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:
200 mg SC once weekly

Number of subjects in period 3	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Started	54	57	67
Completed	41	38	44
Not completed	13	19	23
Consent withdrawn by subject	4	3	4
Physician decision	1	-	2
Adverse event, non-fatal	-	1	2
Sponsor decision, early termination	5	8	9
NK	2	5	5
Lost to follow-up	-	1	1
Protocol deviation	1	-	-
Lack of efficacy	-	1	-

Baseline characteristics

Reporting groups[1]	
Reporting group title	Placebo
Reporting group description:	
Placebo SC, once weekly	
Reporting group title	Tregalizumab 25 mg
Reporting group description:	
Active treatment : Tregalizumab 25 mg SC, once weekly	
Reporting group title	Tregalizumab 100 mg
Reporting group description:	
Active treatment: Tregalizumab 100 mg SC, once weekly	
Reporting group title	Tregalizumab 200 mg
Reporting group description:	
Active treatment: Tregalizumab 200 mg SC, once weekly	

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: The statistical analysis are based on the FAS set, 8 subjects (1x Placebo, 3 x 25mg, 2x 100mg, 2x 200mg) did not fullfill the FAS requirements to receive at least one dose of study medication and have one post-baseline assessment. Therefore instead of 321 sujects randomised only 313 are included in the FAS.

Reporting group values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg
Number of subjects	80	83	80
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Mean Age			
Units: years			
arithmetic mean	53.9	53.7	48.9
standard deviation	± 11.2	± 9.85	± 11.78
Gender categorical Units: Subjects			
Female	66	71	68
Male	13	9	10
Unknown	1	3	2
Race Units: Subjects			
Caucasian	70	69	69
Black/African	0	2	0

American	0	0	0
Asian	0	0	0
Other	9	9	9
Unknown	1	3	2
Functional capacity class Units: Subjects			
Class I	10	10	9
Class II	57	56	60
Class III	12	14	9
Class IV	0	0	0
Unknown	1	3	2
Rheumatoid Factor Units: Subjects			
Positive	57	55	63
Negative	13	15	9
Unknown	10	13	8
BMI Units: kg/m2			
arithmetic mean	27.59	27.24	25.91
standard deviation	± 4.332	± 4.616	± 4.645
Time since diagnosis of Rheumatoid Arthritis Units: Years			
arithmetic mean	7.09	7.08	7.58
standard deviation	± 7.847	± 6.838	± 7.779
Duration of methotrexate treatment Units: Years			
arithmetic mean	2.46	2.22	2.83
standard deviation	± 4.254	± 3.866	± 4.181
Methotrexate dose Units: mg/day			
arithmetic mean	2.36	2.37	2.42
standard deviation	± 0.462	± 0.444	± 0.990

Reporting group values	Tregalizumab 200 mg	Total	
Number of subjects	78	321	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Mean Age			
Units: years			

arithmetic mean	52.8		
standard deviation	± 11.2	-	

Gender categorical Units: Subjects			
Female	58	263	
Male	18	50	
Unknown	2	8	
Race Units: Subjects			
Caucasian	69	277	
Black/African	1	3	
American	0	0	
Asian	0	0	
Other	6	33	
Unknown	2	8	
Functional capacity class Units: Subjects			
Class I	4	33	
Class II	56	229	
Class III	16	51	
Class IV	0	0	
Unknown	2	8	
Rheumatoid Factor Units: Subjects			
Positive	52	227	
Negative	14	51	
Unknown	12	43	
BMI Units: kg/m2			
arithmetic mean	26.77		
standard deviation	± 4.395	-	
Time since diagnosis of Rheumatoid Arthritis Units: Years			
arithmetic mean	7.78		
standard deviation	± 7.426	-	
Duration of methotrexate treatment Units: Years			
arithmetic mean	2.45		
standard deviation	± 2.912	-	
Methotrexate dose Units: mg/day			
arithmetic mean	2.43		
standard deviation	± 0.751	-	

Subject analysis sets

Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS comprised all subjects randomized who received at least one dose of study medication and had at least one post-dose assessment. The FAS was used as the primary analysis set for reporting the analysis of efficacy endpoints.

Subject analysis set title	Safety Set (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety set comprised all subjects who received at least one dose of study medication. The Safety set was used
as the population for the reporting of safety endpoints.

Subject analysis set title	Pharmacokinetic Analysis Set (PKS)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The Pharmacokinetic Analysis Set included all subjects in the SS who have at least one plasma concentration measurement of
tregalizumab.

Subject analysis set title	Per-Protocol Set (PPS)
Subject analysis set type	Per protocol

Subject analysis set description:

The PPS comprised all subjects in the FAS who finished the main phase of the study or terminated the study prematurely in line with the protocol and excluding those with major protocol deviations. Subjects who missed more than two doses of the study medication prior to the primary endpoint at Week 12 did not qualify for the PPS. Subjects must have received the last two study medication injections of Week 10 and Week 11 to qualify for the PPS.

Reporting group values	Full Analysis Set (FAS)	Safety Set (SS)	Pharmacokinetic Analysis Set (PKS)
Number of subjects	313	321	321
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Mean Age			
Units: years arithmetic mean standard deviation	±	±	±
Gender categorical Units: Subjects			
Female Male Unknown	263 50		
Race Units: Subjects			
Caucasian Black/African American	277 3 0		

Asian	0		
Other	33		
Unknown	0		
Functional capacity class Units: Subjects			
Class I	33		
Class II	229		
Class III	51		
Class IV	0		
Unknown	0		
Rheumatoid Factor Units: Subjects			
Positive	227		
Negative	51		
Unknown	35		
BMI Units: kg/m2 arithmetic mean standard deviation	±	±	±
Time since diagnosis of Rheumatoid Arthritis Units: Years arithmetic mean standard deviation	7.38 ± 7.451	±	±
Duration of methotrexate treatment Units: Years arithmetic mean standard deviation	±	±	±
Methotrexate dose Units: mg/day arithmetic mean standard deviation	±	±	±

Reporting group values	Per-Protocol Set (PPS)		
Number of subjects	183		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Mean Age			
Units: years arithmetic mean			

standard deviation	±		

Gender categorical Units: Subjects			
Female Male Unknown			
Race Units: Subjects			
Caucasian Black/African American Asian Other Unknown			
Functional capacity class Units: Subjects			
Class I Class II Class III Class IV Unknown			
Rheumatoid Factor Units: Subjects			
Positive Negative Unknown			
BMI Units: kg/m2 arithmetic mean standard deviation	±		
Time since diagnosis of Rheumatoid Arthritis Units: Years arithmetic mean standard deviation	±		
Duration of methotrexate treatment Units: Years arithmetic mean standard deviation	±		
Methotrexate dose Units: mg/day arithmetic mean standard deviation	±		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Placebo SC, once weekly	
Reporting group title	Tregalizumab 25 mg
Reporting group description: Active treatment : Tregalizumab 25 mg SC, once weekly	
Reporting group title	Tregalizumab 100 mg
Reporting group description: Active treatment: Tregalizumab 100 mg SC, once weekly	
Reporting group title	Tregalizumab 200 mg
Reporting group description: Active treatment: Tregalizumab 200 mg SC, once weekly	
Reporting group title	Placebo
Reporting group description: no active component	
Reporting group title	Tregalizumab 25 mg
Reporting group description: Active treatment	
Reporting group title	Tregalizumab 100 mg
Reporting group description: Active treatment	
Reporting group title	Tregalizumab 200 mg
Reporting group description: Active treatment	
Reporting group title	Tregalizumab 25 mg
Reporting group description: Active treatment	
Reporting group title	Tregalizumab 100 mg
Reporting group description: Active treatment	
Reporting group title	Tregalizumab 200 mg
Reporting group description: -	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description: The FAS comprised all subjects randomized who received at least one dose of study medication and had at least one post-dose assessment. The FAS was used as the primary analysis set for reporting the analysis of efficacy endpoints.	
Subject analysis set title	Safety Set (SS)
Subject analysis set type	Safety analysis
Subject analysis set description: The Safety set comprised all subjects who received at least one dose of study medication. The Safety set was used as the population for the reporting of safety endpoints.	
Subject analysis set title	Pharmacokinetic Analysis Set (PKS)
Subject analysis set type	Sub-group analysis
Subject analysis set description: The Pharmacokinetic Analysis Set included all subjects in the SS who have at least one plasma concentration measurement of	

tregalizumab.

Subject analysis set title	Per-Protocol Set (PPS)
Subject analysis set type	Per protocol

Subject analysis set description:

The PPS comprised all subjects in the FAS who finished the main phase of the study or terminated the study prematurely in line with the protocol and excluding those with major protocol deviations. Subjects who missed more than two doses of the study medication prior to the primary endpoint at Week 12 did not qualify for the PPS. Subjects must have received the last two study medication injections of Week 10 and Week 11 to qualify for the PPS.

Primary: ACR 20 Response rate at Week 12

End point title	ACR 20 Response rate at Week 12

End point description:

Full Analysis Set for observed cases (OC) at Week 12

End point type	Primary

End point timeframe:

0-11 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	71	71	66	70
Units: percentage of subject number	25	30	31	31

Attachments (see zip file)	ACR20/50/70 Response rate at Week 12 (FAS, OC)

Statistical analyses

Statistical analysis title	Statistical Test

Statistical analysis description:

using Chi square test ; If ≥25% of the cells that have expected counts less than 5, stratification will not be taken in to consideration (i.e. Chi-square analysis will be performed). The difference will be presented as a relative risk. There will be no adjustment for multiplicity, which is aligned with the sample size calculation. The analysis will be performed on Observed Cases (OC).

Comparison groups	Tregalizumab 25 mg v Placebo v Tregalizumab 100 mg v Tregalizumab 200 mg
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Confidence interval	
level	95 %
sides	2-sided

Secondary: ACR 20 Response rate at Week 24

End point title	ACR 20 Response rate at Week 24

End point description:

Full analysis Set for observed cases analyses at Week 24, subjects who have moved from Placebo to active
medication or to a higher active dose at Week 12 are presented with their Week 24 response against the treatment they were randomized to at Week 0. It should be noted that 28 of the 72 Placebo subjects were switched to BT061 at Week 12: 18 subjects increased dose from 25 mg to 100 mg and 19 subjects increased dose from 100 to 200 mg.

End point type	Secondary

End point timeframe:

0-24 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	61	56	55
Units: percentage of subject number	35	36	31	31

Statistical analyses

Statistical analysis title	statistical test

Statistical analysis description:

using Chi square test ; If ≥25% of the cells that have expected counts less than 5, stratification will not be taken in to consideration (i.e. Chi-square analysis will be performed). The difference will be presented as a relative risk. There will be no adjustment for multiplicity, which is aligned with the sample size calculation. The analysis will be performed on Observed Cases (OC).

Comparison groups	Placebo v Tregalizumab 25 mg v Tregalizumab 100 mg v Tregalizumab 200 mg
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Confidence interval	
level	95 %
sides	2-sided

Secondary: ACR 50 Response rate at Week 12

End point title	ACR 50 Response rate at Week 12

End point description:

Full Analysis Set for observed cases (OC) at Week 12

End point type	Secondary

End point timeframe:

0-11 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	71	71	66	70
Units: percentage of subject number	7	9	6	9

Statistical analyses

Statistical analysis title	Statistical Test

Statistical analysis description:

using Chi square test ; If ≥25% of the cells that have expected counts less than 5, stratification will not be taken in to consideration (i.e. Chi-square analysis will be performed). The difference will be presented as a relative risk. There will be no adjustment for multiplicity, which is aligned with the sample size calculation. The analysis will be performed on Observed Cases (OC).

Comparison groups	Placebo v Tregalizumab 25 mg v Tregalizumab 100 mg v Tregalizumab 200 mg
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Confidence interval	
level	95 %

Secondary: ACR 50 Response rate at Week 24

End point title	ACR 50 Response rate at Week 24

End point description:

Full analysis Set for observed cases analyses at Week 24, subjects who have moved from Placebo to active
medication or to a higher active dose at Week 12 are presented with their Week 24 response against the treatment they were randomized to at Week 0. It should be noted that 28 of the 72 Placebo subjects were switched to BT061 at Week 12: 18 subjects increased dose from 25 mg to 100 mg and 19 subjects increased dose from 100 to 200 mg.

End point type	Secondary

End point timeframe:

0-24 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	61	56	55
Units: percentage of subject number	13	13	11	11

Statistical analyses

Statistical analysis title	Statistical analysis
Statistical analysis description: using Chi square test ; If ≥25% of the cells that have expected counts less than 5, stratification will not be taken in to consideration (i.e. Chi-square analysis will be performed). The difference will be presented as a relative risk. There will be no adjustment for multiplicity, which is aligned with the sample size calculation. The analysis will be performed on Observed Cases (OC).	
Comparison groups	Placebo v Tregalizumab 25 mg v Tregalizumab 100 mg v Tregalizumab 200 mg
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Confidence interval	
level	95 %

Secondary: ACR 70 Response rate at Week 12

End point title	ACR 70 Response rate at Week 12
End point description: Full Analysis Set for observed cases (OC) at Week 12	
End point type	Secondary
End point timeframe: 0-11 weeks	

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	71	71	66	70
Units: percentage of subject number	1	2	1	3

Statistical analyses

Statistical analysis title	Statistical test

Statistical analysis description:

using Chi square test ; If ≥25% of the cells that have expected counts less than 5, stratification will not be taken in to consideration (i.e. Chi-square analysis will be performed). The difference will be presented as a relative risk. There will be no adjustment for multiplicity, which is aligned with the sample size calculation. The analysis will be performed on Observed Cases (OC).

Comparison groups	Placebo v Tregalizumab 25 mg v Tregalizumab 100 mg v Tregalizumab 200 mg
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Confidence interval	
level	95 %
sides	2-sided

Secondary: ACR 70 Response rate at Week 24

End point title	ACR 70 Response rate at Week 24

End point description:

Full analysis Set for observed cases analyses at Week 24, subjects who have moved from Placebo to active
medication or to a higher active dose at Week 12 are presented with their Week 24 response against the treatment they were randomized to at Week 0. It should be noted that 28 of the 72 Placebo subjects were switched to BT061 at Week 12: 18 subjects increased dose from 25 mg to 100 mg and 19 subjects increased dose from 100 to 200 mg.

End point type	Secondary

End point timeframe:

0-24 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	61	56	55
Units: percentage of subject number	2	6	1	4

Statistical analyses

Statistical analysis title	Statistical test

Statistical analysis description:

using Chi square test ; If ≥25% of the cells that have expected counts less than 5, stratification will not be taken in to consideration (i.e. Chi-square analysis will be performed). The difference will be presented as a relative risk. There will be no adjustment for multiplicity, which is aligned with the sample size calculation. The analysis will be performed on Observed Cases (OC).

Comparison groups	Placebo v Tregalizumab 25 mg v Tregalizumab 100 mg v Tregalizumab 200 mg

Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Confidence interval	
level	95 %
sides	2-sided

Secondary: Proportion of subjects with a DAS28 < 2.6 at Week 12

End point title	Proportion of subjects with a DAS28 < 2.6 at Week 12

End point description:

Percentages are based upon the number of subjects in the full analysis set at Main Phase with a value at the relevant timepoint by treatment group (observed cases).
Subjects are presented according to the treatment they were randomized to at Week 0.

End point type	Secondary

End point timeframe:

0-11 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69	70	66	70
Units: subjects	2	0	0	2

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with a DAS28 <2.6 at Week 24

End point title	Proportion of subjects with a DAS28 <2.6 at Week 24

End point description:

Full analysis Set for observed cases analyses at Week 24, subjects who have moved from Placebo to active medication or to a higher active dose at Week 12 are presented with their Week 24 response against the treatment they were randomized to at Week 0. It should be noted that 28 of the 72 Placebo subjects were switched to BT061 at Week 12: 18 subjects increased dose from 25 mg to 100 mg and 19 subjects increased dose from 100 to 200 mg.

End point type	Secondary

End point timeframe:

0-24 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	44	53	48	48
Units: subjects	0	2	0	4

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with low disease activity at Week 12

End point title	Proportion of subjects with low disease activity at Week 12

End point description:

Percentages are based upon the number of subjects in the full analysis set at Main Phase with a value at the relevant timepoint by treatment group (observed cases). Subjects are presented according to the treatment they were randomized to at Week 0.
Low disease activity was defined as DAS28 <3.2, SDAI ≤11, CDAI ≤10.

End point type	Secondary

End point timeframe:

0-11 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69	69	64	70
Units: subjects	3	2	0	4

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects with Low Disease Activity at Week 24

End point title	Proportion of Subjects with Low Disease Activity at Week 24

End point description:

Low disease activity was defined as DAS28 <3.2, SDAI ≤11, CDAI ≤10.
Percentages are based upon the number of subjects in the full analysis set at Main Phase with a value at the relevant timepoint by treatment group (observed cases). Subjects are presented according to the treatment they were randomized to at Week 0.
Full analysis Set for observed cases analyses at Week 24, subjects who have moved from Placebo to active medication or to a higher active dose at Week 12 are presented with their Week 24 response against the treatment they were randomized to at Week 0. It should be noted that 28 of the 72 Placebo subjects were switched to BT061 at Week 12: 18 subjects increased dose from 25 mg to 100 mg and 19 subjects increased dose from 100 to 200 mg.

End point type	Secondary

End point timeframe:

0-24 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	63	59	53	52
Units: subjects	3	7	1	6

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects in Remission According to the 2011 ACR/EULAR Criteria at Week 12

End point title	Proportion of Subjects in Remission According to the 2011 ACR/EULAR Criteria at Week 12

End point description:

Percentages are based upon the number of subjects in the full analysis set at Main Phase with a value at the relevant timepoint by treatment group (observed cases). Subjects are presented according to the treatment they were randomized to at Week 0.
ACR/EULAR defined remission as tender joint count <=1, swollen joint count <=1, CRP <=1mg/dL and Patient Global Assessment <=1 (on a 0-10 scale).

End point type	Secondary

End point timeframe:

0-11 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69	70	65	70
Units: subjects	1	0	0	1

Statistical analyses

Statistical analysis title	Superiority vs placebo

Statistical analysis description:

Statistical Analysis was based on Fishers Exact Test as >=25% of cells had expected counts of less than 5.

Comparison groups	Tregalizumab 25 mg v Tregalizumab 100 mg v Tregalizumab 200 mg

Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	≤ 0.05 [2]
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Confidence interval	
level	95 %
sides	2-sided

Notes:

[1] - p-value is for comparison of each group vs Placebo.

[2] - the default significant level was < or = 0.05 (5%)

Secondary: Proportion of Subjects in Remission According to the 2011 ACR/EULAR Criteria at Week 24

End point title	Proportion of Subjects in Remission According to the 2011 ACR/EULAR Criteria at Week 24

End point description:

Percentages are based upon the number of subjects in the full analysis set at Main Phase with a value at the relevant timepoint by treatment group (observed cases). Subjects are presented according to the treatment they were randomized to at Week 0.
Full analysis Set for observed cases analyses at Week 24, subjects who have moved from Placebo to active medication or to a higher active dose at Week 12 are presented with their Week 24 response against the treatment they were randomized to at Week 0. It should be noted that 28 of the 72 Placebo subjects were switched to BT061 at Week 12: 18 subjects increased dose from 25 mg to 100 mg and 19 subjects increased dose from 100 to 200 mg.
ACR/EULAR defines remission as Tender joint count <=1, Swollen Joint count <=1, CRP <=1mg/dL and Patient Global Assessment <=1 (on a 0-10 scale).

End point type	Secondary

End point timeframe:

0-24 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	63	59	53	53
Units: subjects	0	0	0	2

Statistical analyses

Statistical analysis title	Fisher’s exact test

Statistical analysis description:

Statistical Analysis was based on Fishers Exact Test as >=25% of cells have expected counts of less than 5.

Comparison groups	Placebo v Tregalizumab 25 mg v Tregalizumab 100 mg v Tregalizumab 200 mg

Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05 [3]
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Confidence interval	
level	95 %
sides	2-sided

Notes:

[3] - The default significant level was < or = 0.05 (5%)

Secondary: Mean change in SDAI at Week 12

End point title	Mean change in SDAI at Week 12

End point description:

Change from baseline was analyzed using an analysis of covariance model with treatment in Main Phase 1 and CRP
level (≤ULN, >ULN) as factors and baseline as a covariate.
Baseline was defined as the last non-missing value prior to first dose of study medication.
Subjects are presented according to the treatment they were randomized to at Week 0.
Change from baseline is defined as value at baseline minus value at post-baseline visit. A positive change/percentage change indicates an improvement.

End point type	Secondary

End point timeframe:

0-11 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69	69	64	70
Units: scores				
arithmetic mean (standard deviation)	14.54 (± 13.223)	16.90 (± 13.121)	13.25 (± 13.718)	13.68 (± 11.188)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in SDAI at Week 24

End point title	Mean change in SDAI at Week 24

End point description:

Change from baseline was analyzed using an analysis of covariance model with treatment in Main Phase 1 and CRP level (≤ULN, >ULN) as factors and baseline as a covariate.
Change from baseline is defined as value at baseline minus value at post-baseline visit. A positive change/percentage change indicates an improvement.

Baseline was defined as the last non-missing value prior to first dose of study medication.
Full analysis Set for observed cases analyses at Week 24, subjects who have moved from Placebo to active medication or to a higher active dose at Week 12 are presented with their Week 24 response against the treatment they were randomized to at Week 0. It should be noted that 28 of the 72 Placebo

subjects were switched to BT061 at Week 12: 18 subjects increased dose from 25 mg to 100 mg and 19 subjects increased dose from 100 to 200 mg.

End point type	Secondary

End point timeframe:

0-24 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	63	59	53	52
Units: scores				
arithmetic mean (standard deviation)	21.17 (± 12.395)	22.78 (± 12.982)	17.73 (± 15.847)	20.03 (± 12.421)

Statistical analyses

Statistical analysis title	Fisher's Exact test
Comparison groups	Placebo v Tregalizumab 25 mg v Tregalizumab 100 mg v Tregalizumab 200 mg
Number of subjects included in analysis	227
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Secondary: Mean Change in CDAI at Week 12

End point title	Mean Change in CDAI at Week 12

End point description:

Change from baseline was analyzed using an analysis of covariance model with treatment in Main Phase 1 and CRP level (≤ULN, >ULN) as factors and baseline as a covariate.
Change from baseline is defined as value at baseline minus value at post-baseline visit. A positive change/percentage change indicates an improvement.

Baseline was defined as the last non-missing value prior to first dose of study medication.
Subjects are presented according to the treatment they were randomized to at Week 0.

End point type	Secondary

End point timeframe:

0-11 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	71	70	65	70
Units: scores				
arithmetic mean (standard deviation)	14.21 (± 13.284)	16.75 (± 13.048)	13.28 (± 13.375)	14.26 (± 10.711)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in CDAI at Week 24

End point title	Mean Change in CDAI at Week 24

End point description:

Change from baseline was analyzed using an analysis of covariance model with treatment in Main Phase 1 and CRP level (≤ULN, >ULN) as factors and baseline as a covariate.
Change from baseline is defined as value at baseline minus value at post-baseline visit. A positive change/percentage change indicates an improvement.

Baseline was defined as the last non-missing value prior to first dose of study medication.
Full analysis Set for observed cases analyses at Week 24, subjects who have moved from Placebo to active medication or to a higher active dose at Week 12 are presented with their Week 24 response against the treatment they were randomized to at Week 0. It should be noted that 28 of the 72 Placebo subjects were switched to BT061 at Week 12: 18 subjects increased dose from 25 mg to 100 mg and 19 subjects increased dose from 100 to 200 mg.

End point type	Secondary

End point timeframe:

0-24 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	61	56	54
Units: scores				
arithmetic mean (standard deviation)	21.46 (± 12.392)	22.72 (± 12.344)	17.95 (± 15.564)	20.13 (± 12.035)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in tender joint counts (68) at Week 12

End point title	Mean Change in tender joint counts (68) at Week 12

End point description:

Baseline was defined as the last non-missing value prior to first dose of study medication.
Change from baseline was defined as value at baseline minus value at post-baseline visit. A positive change indicated an improvement. The maximum tender joint counts was 68.
Subjects were presented according to the treatment they were randomized to at Week 0.

End point type	Secondary

End point timeframe:

0-11 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72	71	66	70
Units: joints				
arithmetic mean (standard deviation)	8.41 (± 10.983)	11.65 (± 10.414)	8.76 (± 10.804)	8.40 (± 9.665)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in tender joint counts (68) at Week 24

End point title	Mean change in tender joint counts (68) at Week 24

End point description:

Baseline was defined as the last non-missing value prior to first dose of study medication.
Change from baseline is defined as value at baseline minus value at post-baseline visit. A positive change indicates an improvement. The maximum tender joint counts was 68.

Full analysis Set for observed cases analyses at Week 24, subjects who have moved from Placebo to active medication or to a higher active dose at Week 12 are presented with their Week 24 response against the treatment they were randomized to at Week 0. It should be noted that 28 of the 72 Placebo subjects were switched to BT061 at Week 12: 18 subjects increased dose from 25 mg to 100 mg and 19 subjects increased dose from 100 to 200 mg.

End point type	Secondary

End point timeframe:

0-24 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	66	61	57	55
Units: joints				
arithmetic mean (standard deviation)	12.89 (± 10.123)	14.72 (± 10.202)	12.56 (± 12.463)	11.98 (± 11.649)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in swollen joint counts (66) at Week 12

End point title	Mean Change in swollen joint counts (66) at Week 12

End point description:

Baseline was defined as the last non-missing value prior to first dose of study medication.
Change from baseline was defined as value at baseline minus value at post-baseline visit.
A positive change indicated an improvement. The maximum swollen joint counts was 66.
Subjects were presented according to the treatment they were randomized to at Week 0.

End point type	Secondary

End point timeframe:

0-11 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72	71	66	70
Units: joints				
arithmetic mean (standard deviation)	6.00 (± 7.571)	8.38 (± 8.171)	7.55 (± 8.294)	7.43 (± 7.789)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in swollen joint counts (66) at Week 24

End point title	Mean Change in swollen joint counts (66) at Week 24

End point description:

Baseline was defined as the last non-missing value prior to first dose of study medication.
Change from baseline is defined as value at baseline minus value at post-baseline visit. A positive change indicated an improvement. The maximum swollen joint counts was 66.

Full analysis Set for observed cases analyses at Week 24, subjects who have moved from Placebo to active medication or to a higher active dose at Week 12 are presented with their Week 24 response against the treatment they were randomized to at Week 0. It should be noted that 28 of the 72 Placebo subjects were switched to BT061 at Week 12: 18 subjects increased dose from 25 mg to 100 mg and 19 subjects increased dose from 100 to 200 mg.

End point type	Secondary

End point timeframe:

0-24 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	66	61	57	55
Units: joints				
arithmetic mean (standard deviation)	9.63 (± 6.673)	10.68 (± 9.067)	10.27 (± 9.928)	8.96 (± 7.164)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in CRP level at Week 12

End point title	Mean Change in CRP level at Week 12

End point description:

Baseline was defined as the last non-missing value prior to first dose of study medication.
Where C-reactive protein (CRP) was reported as <1, i.e. below the lower limit of quantification, this was set equal to 1, the limit of quantification.
Change from baseline was defined as value at baseline minus value at post-baseline visit. A positive change indicated an improvement.Subjects were presented according to the treatment they were randomized to at Week 0.

End point type	Secondary

End point timeframe:

0-11 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	70	71	67	70
Units: mg/L				
arithmetic mean (standard deviation)	0.5 (± 13.73)	-2.4 (± 10.96)	-0.9 (± 14.51)	-5.7 (± 20.02)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in CRP level at Week 24

End point title	Mean Change in CRP level at Week 24

End point description:

Baseline was defined as the last non-missing value prior to first dose of study medication.
Where C-reactive protein (CRP)was reported as <1, i.e. below the lower limit of quantification, this was set equal to 1, the limit of quantification.

Change from baseline was defined as value at baseline minus value at post-baseline visit. A positive change indicated an improvement.
Subjects were presented according to the treatment they were randomized to at Week 0.
Full analysis Set for observed cases analyses at Week 24, subjects who have moved from Placebo to active medication or to a higher active dose at Week 12 are presented with their Week 24 response against the treatment they were randomized to at Week 0. It should be noted that 28 of the 72 Placebo subjects were switched to BT061 at Week 12: 18 subjects increased dose from 25 mg to 100 mg and 19 subjects increased dose from 100 to 200 mg.

End point type	Secondary

End point timeframe:

0-24 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	64	59	54	53
Units: mg/L				
arithmetic mean (standard deviation)	-1.2 (± 17.51)	-1.2 (± 13.35)	-0.4 (± 11.56)	-0.5 (± 13.71)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in Erythrocyte Sedimentation Rate (ESR) at Week 12

End point title	Mean Change in Erythrocyte Sedimentation Rate (ESR) at Week 12

End point description:

Baseline was defined as the last non-missing value prior to first dose of study medication.
Change from baseline was defined as value at baseline minus value at post-baseline visit. A positive change indicated an improvement.
Subjects were presented according to the treatment they were randomized to at Week 0.

End point type	Secondary

End point timeframe:

0-11 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	70	71	68	70
Units: mm/h				
arithmetic mean (standard deviation)	12.1 (± 13.93)	14.8 (± 46.03)	10.2 (± 26.67)	9.9 (± 24.25)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in Erythrocyte Sedimentation Rate (ESR) at Week 24

End point title	Mean Change in Erythrocyte Sedimentation Rate (ESR) at Week 24

End point description:

Baseline was defined as the last non-missing value prior to first dose of study medication.
Change from baseline is defined as value at baseline minus value at post-baseline visit. A positive change indicates an improvement.
Full analysis Set for observed cases analyses at Week 24, subjects who have moved from Placebo to active medication or to a higher active dose at Week 12 are presented with their Week 24 response against the treatment they were randomized to at Week 0. It should be noted that 28 of the 72 Placebo subjects were switched to BT061 at Week 12: 18 subjects increased dose from 25 mg to 100 mg and 19 subjects increased dose from 100 to 200 mg.

End point type	Secondary

End point timeframe:

0-24 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	66	60	56	53
Units: mm/h				
arithmetic mean (standard deviation)	12.3 (± 15.99)	17.5 (± 50.79)	10.7 (± 24.92)	10.0 (± 18.66)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in subject’s global assessment of pain at Week 12

End point title	Change in subject’s global assessment of pain at Week 12

End point description:

Baseline was defined as the last non-missing value prior to first dose of study medication.
Change from baseline was defined as value at baseline minus value at post-baseline visit. A positive change indicated an improvement.
Subjects were presented according to the treatment they were randomized to at Week 0.
The subject was asked to assess his or her current level of pain in the past week by marking a vertical tick on a 100 mm horizontal VAS with the left end marked as “no pain” and the right end marked as “worst possible pain”, where the maximum possible value is 100 mm.

End point type	Secondary

End point timeframe:

0-11 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	71	72	69	70
Units: visual analog scales (VAS)				
arithmetic mean (standard deviation)	13.5 (± 19.52)	13.1 (± 26.80)	10.4 (± 22.08)	11.0 (± 25.34)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in subject’s global assessment of pain at Week 24

End point title	Change in subject’s global assessment of pain at Week 24

End point description:

Baseline was defined as the last non-missing value prior to first dose of study medication.
Change from baseline is defined as value at baseline minus value at post-baseline visit. A positive change indicates an improvement.
Full analysis Set for observed cases analyses at Week 24, subjects who have moved from Placebo to active medication or to a higher active dose at Week 12 are presented with their Week 24 response against the treatment they were randomized to at Week 0. It should be noted that 28 of the 72 Placebo subjects were switched to BT061 at Week 12: 18 subjects increased dose from 25 mg to 100 mg and 19 subjects increased dose from 100 to 200 mg.
The subject was asked to assess his or her current level of pain in the past week by marking a vertical tick on a 100 mm horizontal VAS with the left end marked as “no pain” and the right end marked as “worst possible pain”, where the maximum possible value is 100 mm.

End point type	Secondary

End point timeframe:

0-24 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	61	57	56
Units: visual analog scale (VAS)				
arithmetic mean (standard deviation)	18.8 (± 22.95)	16.8 (± 26.67)	12.5 (± 24.49)	15.9 (± 25.07)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in subject's global assessment of disease activity at Week 12

End point title	Change in subject's global assessment of disease activity at Week 12

End point description:

Baseline was defined as the last non-missing value prior to first dose of study medication.
Subjects were presented according to the treatment they were randomized to at Week 0.

The subject’s overall assessment of his or her disease activity during the last 24 hours was recorded

using the 100 mm horizontal VAS where the left end represents no disease activity (symptom free and no arthritis symptoms) and the right end represents maximum disease activity (maximum arthritis disease activity), where the maximum possible value is 100 mm.
The subject was asked to give an overall assessment of how the arthritis is affecting them at present by marking a vertical tick on a VAS from "no arthritis activity" to "extremely active arthritis".

Change from baseline was defined as value at baseline minus value at post-baseline visit. A positive change indicated an improvement.

End point type	Secondary

End point timeframe:

0-11 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	71	72	69	70
Units: visual analog scale (VAS)				
arithmetic mean (standard deviation)	15.0 (± 18.39)	16.8 (± 25.04)	9.3 (± 21.11)	12.8 (± 26.19)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in subject's global assessment of disease activity at Week 24

End point title	Change in subject's global assessment of disease activity at Week 24

End point description:

Baseline was defined as the last non-missing value prior to first dose of study medication.
Subjects were presented according to the treatment they were randomized to at Week 0. It should be noted that 28 of the 72 Placebo subjects were switched to BT061 at Week 12: 18 subjects increased dose from 25 mg to 100 mg and 19 subjects increased dose from 100 to 200 mg.
The subject's overall assessment of his or her disease activity during the last 24 h was recorded using the 100 mm horizontal VAS where the left end represents no disease activity (symptom free and no arthritis symptoms) and the right end represents maximum disease activity (maximum arthritis disease activity), where the maximum possible value is 100 mm.
Change from baseline was defined as value at baseline minus value at post-baseline visit. A positive change indicated an improvement.

End point type	Secondary

End point timeframe:

0-24 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	46	42	42
Units: visual analoge scale (VAS)				
arithmetic mean (standard deviation)	19.8 (± 23.11)	20.3 (± 24.38)	14.8 (± 25.78)	16.7 (± 21.45)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Physician's global assessment of disease activity at Week 12

End point title	Change in Physician's global assessment of disease activity at Week 12

End point description:

Baseline was defined as the last non-missing value prior to first dose of study medication.
Subjects were presented according to the treatment they were randomized to at Week 0.
The physician’s assessment of a subject’s disease activity during the last 24 hours was recorded using the 100 mm horizontal VAS. Results will be expressed in millimeters measured between the left end of the scale and the crossing point of the vertical line of the tick, where the maximum possible value was 100 mm.
Change from baseline was defined as value at baseline minus value at post-baseline visit. A positive change indicated an improvement.

End point type	Secondary

End point timeframe:

0-11 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	71	71	68	70
Units: mm (VAS)				
arithmetic mean (standard deviation)	20.0 (± 19.11)	22.7 (± 22.16)	21.0 (± 16.94)	20.0 (± 20.90)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Physician's global assessment of disease activity at Week 24

End point title	Change in Physician's global assessment of disease activity at Week 24

End point description:

Baseline was defined as the last non-missing value prior to first dose of study medication.
Subjects were presented according to the treatment they were randomized to at Week 0. It should be noted that 28 of the 72 Placebo subjects were switched to BT061 at Week 12: 18 subjects increased dose from 25 mg to 100 mg and 19 subjects increased dose from 100 to 200 mg.
The physician’s assessment of a subject’s disease activity during the last 24 hours was recorded using the 100 mm horizontal VAS. Results will be expressed in millimeters measured between the left end of the scale and the crossing point of the vertical line of the tick, where the maximum possible value was 100 mm.
Change from baseline was defined as value at baseline minus value at post-baseline visit. A positive

change indicated an improvement.

End point type	Secondary
End point timeframe:	
0-24 weeks	

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	61	57	55
Units: mm (VAS)				
arithmetic mean (standard deviation)	31.5 (± 20.71)	32.0 (± 21.53)	28.6 (± 23.17)	33.9 (± 21.22)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Health Assessment Questionnaire Disability Index (HAQ-DI) at Week 12

End point title	Change in Health Assessment Questionnaire Disability Index (HAQ-DI) at Week 12

End point description:

Baseline was defined as the last non-missing value prior to first dose of study medication.
Subjects were presented according to the treatment they were randomized to at Week 0.
The HAQ-DI is a questionnaire comprising of 20 items assessing each of 8 functional areas (dressing and grooming, arising, eating, walking, hygiene, reach, grip and activities). For each item, there is a four-level response set that is scored from 0 (no difficulty) to 3 (unable to perform activity) that measures the ability to perform (daily) activities over the previous week.
Total score is between 0–3.0, in 0.125 increments. Increasing scores indicate worse functioning with 0 indicating no functional impairment and 3 indicating complete impairment.
Change from baseline was defined as value at baseline minus value at post-baseline visit. A positive change indicated an improvement.

End point type	Secondary
End point timeframe:	
0-11 weeks	

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	71	72	69	70
Units: scores				
arithmetic mean (standard deviation)	0.22 (± 0.424)	0.26 (± 0.635)	0.22 (± 0.423)	0.15 (± 0.607)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Health Assessment Questionnaire Disability Index (HAQ-DI) at Week 24

End point title	Change in Health Assessment Questionnaire Disability Index (HAQ-DI) at Week 24

End point description:

Baseline was defined as the last non-missing value prior to first dose of study medication.
Subjects were presented according to the treatment they were randomized to at Week 0. It should be noted that 28 of the 72 Placebo subjects were switched to BT061 at Week 12: 18 subjects increased dose from 25 mg to 100 mg and 19 subjects increased dose from 100 to 200 mg.
The HAQ-DI is a questionnaire comprising of 20 items assessing each of 8 functional areas (dressing and grooming, arising, eating, walking, hygiene, reach, grip and activities). For each item, there is a four-level response set that is scored from 0 (no difficulty) to 3 (unable to perform activity) that measures the ability
to perform (daily) activities over the previous week.
Total score is between 0–3.0, in 0.125 increments. Increasing scores indicate worse functioning with 0 indicating no functional impairment and 3 indicating complete impairment.
Change from baseline was defined as value at baseline minus value

End point type	Secondary

End point timeframe:

0-24 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	61	57	56
Units: scores				
arithmetic mean (standard deviation)	0.29 (± 0.466)	0.41 (± 0.653)	0.24 (± 0.620)	0.31 (± 0.534)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in duration of Morning Stiffness at Week 12

End point title	Change in duration of Morning Stiffness at Week 12

End point description:

Baseline was defined as the last non-missing value prior to first dose of study medication.
Subjects were presented according to the treatment they were randomized to at Week 0.
Subjects were asked about duration of morning stiffness on the day prior to the study visit to capture actual symptoms.
Change from baseline was defined as value at baseline minus value at post-baseline visit. A positive change indicated an improvement.

End point type	Secondary

End point timeframe:

0-11 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	71	72	69	70
Units: minute				
arithmetic mean (standard deviation)	50.9 (± 79.73)	34.8 (± 127.63)	56.0 (± 166.32)	42.7 (± 122.07)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in duration of Morning Stiffness at Week 24

End point title	Change in duration of Morning Stiffness at Week 24

End point description:

Baseline was defined as the last non-missing value prior to first dose of study medication.
Subjects were presented according to the treatment they were randomized to at Week 0. It should be noted that 28 of the 72 Placebo subjects were switched to BT061 at Week 12: 18 subjects increased dose from 25 mg to 100 mg and 19 subjects increased dose from 100 to 200 mg.
Subjects were asked about duration of morning stiffness on the day prior to the study visit to capture actual symptoms.
Change from baseline was defined as value at baseline minus value at post-baseline visit. A positive change indicated an improvement.

End point type	Secondary

End point timeframe:

0-24 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	61	57	56
Units: minute				
arithmetic mean (standard deviation)	48.1 (± 95.05)	41.8 (± 174.42)	73.7 (± 208.88)	23.2 (± 208.70)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in functional assessment of chronic illness therapy-fatigue scale (FACIT-Fatigue) at Week 12

End point title	Change in functional assessment of chronic illness therapy-fatigue scale (FACIT-Fatigue) at Week 12

End point description:

Baseline was defined as the last non-missing value prior to first dose of study medication.
Subjects were presented according to the treatment they were randomized to at Week 0.
FACIT-F is a self-assessment questionnaire measuring fatigue in subjects with RA.
It consists of 13 questions rated on a 5-point scale (0=not at all, 1=a little bit, 2=somewhat, 3=quite a

bit, 4=very much). Except for items "I have energy" and "I am able to do my usual activities", the responses are reversed (i.e.4 becomes 0), to calculate the total score. The scores for the individual items are summed
to provide a total FACIT- fatigue score. Score range 0-52. A score of less than 30 indicates severe fatigue.
The higher the score, the better the quality of life.
Change from baseline was defined as value at post-baseline visit minus value at baseline. A positive change indicated an improvement.

End point type	Secondary

End point timeframe:

0-11 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	71	72	69	70
Units: scores				
arithmetic mean (standard deviation)	4.6 (± 9.22)	4.8 (± 10.84)	4.0 (± 7.50)	4.5 (± 9.15)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in functional assessment of chronic illness therapy-fatigue scale (FACIT-Fatigue) at Week 24

End point title	Change in functional assessment of chronic illness therapy-fatigue scale (FACIT-Fatigue) at Week 24

End point description:

Baseline was defined as the last non-missing value prior to first dose of study medication.
Subjects were presented according to the treatment they were randomized to at Week 0. It should be noted that 28 of the 72 Placebo subjects were switched to BT061 at Week 12: 18 subjects increased dose from 25 mg to 100 mg and 19 subjects increased dose from 100 to 200 mg.
FACIT-F is a self-assessment questionnaire measuring fatigue in subjects with RA. Score range 0-52. A score of less than 30 indicates severe fatigue.
The higher the score, the better the quality of life.
Change from baseline was defined as value at post-baseline visit minus value at baseline. A positive change indicated an improvement.

End point type	Secondary

End point timeframe:

0-24 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	61	57	56
Units: scores				
arithmetic mean (standard deviation)	6.3 (± 9.76)	8.0 (± 10.98)	5.5 (± 11.44)	6.4 (± 9.95)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in SF-36 Physical Component Score at Week 12

End point title	Change in SF-36 Physical Component Score at Week 12

End point description:

Baseline was defined as the last non-missing value prior to first dose of study medication.
Subjects were presented according to the treatment they were randomized to at Week 0.
The SF-36 is a short-form health survey consisting of 36 questions, yielding eight health-related quality of life domains: physical functioning, role-physical, bodily pain, general health, vitality, social function, role-emotional, mental health. A higher score represents better quality of life.
Change from baseline was defined as value at post-baseline visit minus value at baseline. A positive change indicated an improvement.

End point type	Secondary

End point timeframe:

0-11 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	71	72	69	70
Units: scores				
arithmetic mean (standard deviation)	4.12 (± 6.368)	4.70 (± 7.906)	2.83 (± 6.864)	3.72 (± 8.326)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in SF-36 Physical Component Score at Week 24

End point title	Change in SF-36 Physical Component Score at Week 24

End point description:

Baseline was defined as the last non-missing value prior to first dose of study medication.
Subjects were presented according to the treatment they were randomized to at Week 0. It should be noted that 28 of the 72 Placebo subjects were switched to BT061 at Week 12: 18 subjects increased dose from 25 mg to 100 mg and 19 subjects increased dose from 100 to 200 mg.

The SF-36 is a short-form health survey consisting of 36 questions, yielding eight health-related quality of life domains: physical functioning, role-physical, bodily pain, general health, vitality, social function, role-emotional, mental health. A higher score represents better quality of life.
Change from baseline was defined as value at post-baseline visit minus value at baseline. A positive change indicated an improvement.

End point type	Secondary

End point timeframe:

0-24 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	61	57	56
Units: scores				
arithmetic mean (standard deviation)	6.05 (± 7.342)	5.23 (± 9.558)	3.81 (± 6.903)	4.33 (± 7.655)

Statistical analyses

No statistical analyses for this end point

Secondary: DAS28 EULAR response at Week12

End point title	DAS28 EULAR response at Week12

End point description:

Baseline was defined as the last non-missing value prior to first dose of study medication.
Subjects were presented according to the treatment they were randomized to at Week 0.
Disease Activity Score 28 =DAS28 ;European League Against Rheumatism =EULAR
DAS28 is measured on a continuous scale ranging from 0 to 9.4. The level of disease activity is interpreted as low (DAS28 <3.2), moderate (3.2 ≤ DAS28 ≤ 5.1), and high (DAS28 >5.1). A DAS28 <2.6
corresponds to being in remission. A Reduction from scores at baseline means improvement.
Improvements in DAS 28 were categorized using the DAS28 EULAR response criteria as Good response or Moderate response or No response.

End point type	Secondary

End point timeframe:

0-11 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69	70	66	70
Units: subjects				
Good response	5	2	0	4
Moderate response	30	42	41	37

Statistical analyses

No statistical analyses for this end point

Secondary: DAS28 EULAR response at Week 24

End point title	DAS28 EULAR response at Week 24

End point description:

Baseline was defined as the last non-missing value prior to first dose of study medication.
Subjects were presented according to the treatment they were randomized to at Week 0. It should be noted that 28 of the 72 Placebo subjects were switched to BT061 at Week 12: 18 subjects increased dose from 25 mg to 100 mg and 19 subjects increased dose from 100 to 200 mg.
Disease Activity Score 28 =DAS28 ;European League Against Rheumatism =EULAR
DAS28 is measured on a continuous scale ranging from 0 to 9.4. The level of disease activity is interpreted as low (DAS28 <3.2), moderate (3.2 ≤ DAS28 ≤ 5.1), and high (DAS28 >5.1). A DAS28 <2.6 corresponds to being in remission. A Reduction from scores at baseline means improvement.
Improvements in DAS 28 were categorized using the DAS28 EULAR response criteria as Good response or Moderate response or No response.

End point type	Secondary

End point timeframe:

0-24 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	60	53	53
Units: subjects				
Good response	6	9	1	6
Moderate response	46	37	34	34

Statistical analyses

No statistical analyses for this end point

Secondary: BT061 Plasma levels at Week 12

End point title	BT061 Plasma levels at Week 12[4]

End point description:

In order to study the BT061 PK profile, blood samples for the determination of BT061 plasma levels will be taken prior to the administration of study drug at specified visit.
Subjects were presented according to the treatment they were randomized to at Week 0.

End point type	Secondary

End point timeframe:

0-11 weeks

Notes:

[4] - 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 values for Tregalizumab Plasma Levels are available for the placebo group as these did not receive active treatment.

End point values	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	53	48	47	
Units: ng/mL				
arithmetic mean (standard deviation)	12.61 (± 2.589)	30.85 (± 53.542)	3605.29 (± 8092.025)	

Statistical analyses

No statistical analyses for this end point

Secondary: BT061 Plasma levels at Week 24

End point title	BT061 Plasma levels at Week 24

End point description:

In order to study the BT061 PK profile, blood samples for the determination of BT061 plasma levels were taken prior to the administration of study drug at the specified times.
Subjects were presented according to the treatment they were randomized to at Week 0.
It should be noted that 28 of the 72 Placebo subjects were switched to BT061 at Week 12: 18 subjects increased dose from 25 mg to 100 mg and 19 subjects increased dose from 100 to 200 mg.

End point type	Secondary

End point timeframe:

0-24 weeks

End point values	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45	41	38	
Units: ng/mL				
arithmetic mean (standard deviation)	12.74 (± 3.287)	76.32 (± 213.096)	3876.53 (± 8604.606)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in CD3CD4 Cell Counts at Week 12

End point title	Percent Change in CD3CD4 Cell Counts at Week 12

End point description:

Mean Percent Change from Baseline of CD3CD4 Cell Counts at Week 12.

Baseline was defined as the last non-missing value prior to first dose of study medication.
Subjects were presented according to the treatment they were randomized to at Week 0.

End point type	Secondary

End point timeframe:

0-11 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	69	63	62
Units: cells/microlitre				
arithmetic mean (standard deviation)	7.350 (± 35.759)	-2.882 (± 31.810)	-6.732 (± 39.299)	-22.502 (± 33.949)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with CD4 Counts of Lymphocytes <400 cells/µL during Main Phase 1

End point title	Number of Subjects with CD4 Counts of Lymphocytes <400 cells/µL during Main Phase 1

End point description:

Baseline was defined as the last non-missing value prior to first dose of study medication.
Subjects were presented according to the treatment they were randomized to at Week 0.
Number of Subjects with CD4 Counts of Lymphocytes <400 cells/µL at Least Once or at Least Twice during the Main Phase 1.

End point type	Secondary

End point timeframe:

0-11 weeks

End point values	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg	Tregalizumab 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	83	80	78
Units: subjects				
<400 at Least Once	5	9	13	14
<400 at Least Twice	0	1	4	6

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

0-48 weeks

Adverse event reporting additional description:

Adverse events (AEs) were coded using MedDRA central coding dictionary, Version 17.1.
Treatment emergent AEs (TEAEs) are defined as AEs that started or worsened in severity on or after the first dose of study medication until the date of the subject's last study visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo
Safety population

Reporting group title	Tregalizumab 25 mg

Reporting group description:

Active treatment

Reporting group title	Tregalizumab 100 mg

Reporting group description:

Active treatment

Reporting group title	Tregalizumab 200 mg

Reporting group description:

Active treatment

Serious adverse events	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 80 (1.25%)	2 / 105 (1.90%)	1 / 117 (0.85%)
number of deaths (all causes)	0	1	1
number of deaths resulting from adverse events	0	1	1
Investigations			
Flavivirus test positive			
subjects affected / exposed	1 / 80 (1.25%)	0 / 105 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Road traffic accident			

subjects affected / exposed	0 / 80 (0.00%)	0 / 105 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple injuries			
subjects affected / exposed	0 / 80 (0.00%)	0 / 105 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Frostbite	Additional description: occurred in Extension Phase		
subjects affected / exposed	0 / 80 (0.00%)	0 / 105 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Shock hemorrhagic			
subjects affected / exposed	0 / 80 (0.00%)	0 / 105 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 80 (0.00%)	1 / 105 (0.95%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Nervous system disorders			
Multiple sclerosis			
subjects affected / exposed	1 / 80 (1.25%)	0 / 105 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalized tonic-clonic seizure			
subjects affected / exposed	0 / 80 (0.00%)	0 / 105 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral hemorrhage	Additional description: occurred in Extension Phase		
subjects affected / exposed	0 / 80 (0.00%)	0 / 105 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General disorders and administration site conditions			
Death unknown cause			
subjects affected / exposed	0 / 80 (0.00%)	0 / 105 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 80 (0.00%)	1 / 105 (0.95%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal hernia			
subjects affected / exposed	0 / 80 (0.00%)	0 / 105 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Lichen planus			
subjects affected / exposed	0 / 80 (0.00%)	0 / 105 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 80 (0.00%)	0 / 105 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteoarthritis (exacerbation)	Additional description: occured in Extension Phase		
subjects affected / exposed	0 / 80 (0.00%)	1 / 105 (0.95%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Peritonitis			
subjects affected / exposed	0 / 80 (0.00%)	1 / 105 (0.95%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gangrene	Additional description: occurred in Extension Phase		
subjects affected / exposed	0 / 80 (0.00%)	0 / 105 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Tregalizumab 200 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 122 (5.74%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Investigations			
Flavivirus test positive			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Road traffic accident			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Multiple injuries			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Frostbite	Additional description: occurred in Extension Phase		
subjects affected / exposed	1 / 122 (0.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Shock hemorrhagic			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute coronary syndrome			

subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Multiple sclerosis			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Generalized tonic-clonic seizure			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral hemorrhage	Additional description: occurred in Extension Phase		
subjects affected / exposed	1 / 122 (0.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Death unknown cause			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal disorders			
Colitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal hernia			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Lichen planus			

subjects affected / exposed	1 / 122 (0.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteoarthritis (exacerbation)	Additional description: occured in Extension Phase		
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Peritonitis			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gangrene	Additional description: occurred in Extension Phase		
subjects affected / exposed	1 / 122 (0.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo	Tregalizumab 25 mg	Tregalizumab 100 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 80 (11.25%)	15 / 105 (14.29%)	18 / 117 (15.38%)
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 80 (3.75%)	3 / 105 (2.86%)	6 / 117 (5.13%)
occurrences (all)	3	4	9
Musculoskeletal and connective tissue disorders			

Rheumatoid arthritis subjects affected / exposed occurrences (all)	2 / 80 (2.50%) 3	5 / 105 (4.76%) 5	6 / 117 (5.13%) 6
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	4 / 80 (5.00%) 4	7 / 105 (6.67%) 9	6 / 117 (5.13%) 6

Non-serious adverse events	Tregalizumab 200 mg		
Total subjects affected by non-serious adverse events subjects affected / exposed	18 / 122 (14.75%)		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	6 / 122 (4.92%) 6		
Musculoskeletal and connective tissue disorders Rheumatoid arthritis subjects affected / exposed occurrences (all)	5 / 122 (4.10%) 5		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	7 / 122 (5.74%) 10		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 October 2013	Global, version 3.0: 1. In response to the FDA and German regulatory (Paul-Ehrlich-Institut) recommendations an additional step was added to discontinue patients who do not have 20% improvement from baseline in TJC and SJC at Week 24. 2. The auto-injection device will no longer be used in the study, therefore all reference has been deleted. 3. It was clarified that an additional 12 mL of blood will be taken for the predictive bioassay at selected sites only. 4. It was clarified that a DAS28 less than 2.6 corresponds to being in remission, not less than or equal to. 5. It was clarified that samples will be stored for up to 15 years. 6. Minor corrections, clarifications and administrative changes including staff changes in the study management. 7. Incorporation of the non-substantial amendment 1.

03 December 2014	Final Protocol (version 4/4.1; 03 Dec 2014) 1. Removal of baseline check for exclusion criterion 15: Subject has an acute or clinically symptomatic Epstein-Barr virus (EBV) or cytomegalovirus (CMV) infection, as the baseline laboratory results will not be available at the time of randomization. 2. Clarification that HBV, HCV, HIV, EBV and CMV blood samples taken at Visit 2 are retention samples only. 3. Clarification of EBV serology assessment in case of positive PCR result only. 4. Clarification of CMV serology assessment in case of positive PCR result only. 5. Addition to clarify that unused pharmacokinetic backup plasma samples may be used to measure soluble CD4 (sCD4), as an additional optional analytical variable. 6. Clarification that laboratory samples for EBV and CMV at FU Visit/EoT will be taken as retention samples only. 7. Clarification of tregalizumab storage conditions. 8. Correction of the typographical error for the definition of DAS28 low disease activity to DAS28 <3.2 and not DAS28 ≤3.2. 9. Correction of information relating to temperature measurement i.e., removal of requirement to record region used in the eCRF and removal of reference to tympanic measurements. 10. Correction of information relating to the visit schedule Week 6/Visit 6 as no drug will be dispensed at this visit as correctly indicated in the flowchart. 11. Correction of information relating to the visit schedule as the subject diary will only be dispensed once in this study at Week 2/Visit 4. 12. Replacement of the Medical Manager Thorsten Holzkämper with Andrea Wartenberg-Demand and Xuefei Zhou, and replacement of the Statistician Dermot Whyms with Vanessa Steele.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
31 July 2015	The Extension Phase of the study was terminated early on the 31 July 2015 due to lack of clinical efficacy.	-

Notes:

Limitations and caveats

None reported