



Clinical trial results:

A Phase IIb, Randomized, Multi-Center, Double-Blind, Dose-Ranging Study to Evaluate the Efficacy and Safety of Clazakizumab in Subjects With Moderate to Severe Active Rheumatoid Arthritis Who Have Experienced an Inadequate Response to TNF Inhibitors

Summary

EudraCT number	2013-003780-65
Trial protocol	IT HU
Global end of trial date	17 June 2015

Results information

Result version number	v1 (current)
This version publication date	05 January 2019
First version publication date	05 January 2019

Trial information

Trial identification

Sponsor protocol code	IM133-066
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, clinical.trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 June 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	17 June 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to compare the efficacy of clazakizumab versus placebo on a background of methotrexate as assessed by change from baseline in DAS28-CRP at 12 weeks in subjects with moderate to severe active rheumatoid arthritis who have an inadequate response to TNF inhibitors (TNF-IR)

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 January 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 38
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	South Africa: 12
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Hungary: 22
Country: Number of subjects enrolled	Mexico: 29
Country: Number of subjects enrolled	Argentina: 18
Country: Number of subjects enrolled	Japan: 16
Worldwide total number of subjects	143
EEA total number of subjects	25

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)	114
From 65 to 84 years	28
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

216 subjects were enrolled. 143 subjects were randomized.

Period 1

Period 1 title	12 Week Double Blind Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
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Arm title	PBO + MTX
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Arm description:

Clazakizumab placebo SC every 4 weeks with background methotrexate

Arm type	Placebo
Investigational medicinal product name	Clazakizumab placebo
Investigational medicinal product code	BMS-945429 Placebo
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Clazakizumab placebo SC every 4 weeks with background methotrexate

Arm title	C1 + MTX
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Arm description:

Clazakizumab 1 mg SC every 4 weeks with background methotrexate

Arm type	Experimental
Investigational medicinal product name	Clazakizumab
Investigational medicinal product code	BMS-945429
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Clazakizumab 1 mg SC every 4 weeks with background methotrexate

Arm title	C5 + MTX
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Arm description:

Clazakizumab 5 mg SC every 4 weeks with background methotrexate

Arm type	Experimental
Investigational medicinal product name	Clazakizumab
Investigational medicinal product code	BMS-945429
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Clazakizumab 5 mg SC every 4 weeks with background methotrexate

Arm title	C25 + MTX
Arm description: Clazakizumab 25 mg SC every 4 weeks with background methotrexate	
Arm type	Experimental
Investigational medicinal product name	Clazakizumab
Investigational medicinal product code	BMS-945429
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Clazakizumab 25 mg SC every 4 weeks with background methotrexate

Number of subjects in period 1	PBO + MTX	C1 + MTX	C5 + MTX
Started	40	21	42
Completed	19	8	17
Not completed	21	13	25
Adverse event, serious fatal	1	-	-
Subject request to discontinue treatment	1	1	2
Consent withdrawn by subject	2	2	1
Adverse event, non-fatal	-	-	-
LTE -- other	1	1	-
Completed DB and cont. to follow-up	14	8	16
LTE -- sponsor reason	-	-	1
Completed DB, not dosed in LTE	1	-	-
LTE -- withdrew consent	-	-	1
Lost to follow-up	-	-	1
Subject no longer meets study criteria	-	1	-
Lack of efficacy	1	-	3

Number of subjects in period 1	C25 + MTX
Started	40
Completed	19
Not completed	21
Adverse event, serious fatal	-
Subject request to discontinue treatment	1
Consent withdrawn by subject	-
Adverse event, non-fatal	1
LTE -- other	-
Completed DB and cont. to follow-up	17

LTE -- sponsor reason	-
Completed DB, not dosed in LTE	-
LTE -- withdrew consent	-
Lost to follow-up	-
Subject no longer meets study criteria	-
Lack of efficacy	2

Period 2

Period 2 title	Open Label Long Term Extension
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	PBO + MTX

Arm description:

Clazakizumab placebo SC every 4 weeks with background methotrexate

Arm type	Placebo
Investigational medicinal product name	Clazakizumab placebo
Investigational medicinal product code	BMS-945429 Placebo
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Clazakizumab placebo SC every 4 weeks with background methotrexate

Arm title	C1 + MTX
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Arm description:

Clazakizumab 1 mg SC every 4 weeks with background methotrexate (n = 20)

Arm type	Experimental
Investigational medicinal product name	Clazakizumab
Investigational medicinal product code	BMS-945429
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Clazakizumab 1 mg SC every 4 weeks with background methotrexate

Arm title	C5 + MTX
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Arm description:

Clazakizumab 5 mg SC every 4 weeks with background methotrexate

Arm type	Experimental
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Investigational medicinal product name	Clazakizumab
Investigational medicinal product code	BMS-945429
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
Clazakizumab 5 mg SC every 4 weeks with background methotrexate	
Arm title	C25 + MTX

Arm description:

Clazakizumab 25 mg SC every 4 weeks with background methotrexate

Arm type	Experimental
Investigational medicinal product name	Clazakizumab
Investigational medicinal product code	BMS-945429
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Clazakizumab 25 mg SC every 4 weeks with background methotrexate

Number of subjects in period 2	PBO + MTX	C1 + MTX	C5 + MTX
Started	19	8	17
Completed	0	1	0
Not completed	19	7	17
Consent withdrawn by subject	1	-	-
Adverse event, non-fatal	-	-	-
Ongoing in LTE as of Apr2015	3	1	2
Sponsor reason	15	6	15

Number of subjects in period 2	C25 + MTX
Started	19
Completed	1
Not completed	18
Consent withdrawn by subject	-
Adverse event, non-fatal	1
Ongoing in LTE as of Apr2015	4
Sponsor reason	13

Baseline characteristics

Reporting groups

Reporting group title	PBO + MTX
Reporting group description:	
Clazakizumab placebo SC every 4 weeks with background methotrexate	
Reporting group title	C1 + MTX
Reporting group description:	
Clazakizumab 1 mg SC every 4 weeks with background methotrexate	
Reporting group title	C5 + MTX
Reporting group description:	
Clazakizumab 5 mg SC every 4 weeks with background methotrexate	
Reporting group title	C25 + MTX
Reporting group description:	
Clazakizumab 25 mg SC every 4 weeks with background methotrexate	

Reporting group values	PBO + MTX	C1 + MTX	C5 + MTX
Number of subjects	40	21	42
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	32	15	35
From 65-84 years	8	6	6
85 years and over	0	0	1
Age Continuous Units: years			
arithmetic mean	54.4	55.8	53.4
standard deviation	± 11.21	± 11.20	± 13.75
Gender Categorical Units: Subjects			
Female	35	18	33
Male	5	3	9
Race (NIH/OMB) Units: Subjects			
White	30	18	34
Black or African American	1	0	2
Asian	5	3	5
Other	4	0	1
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic/Latino	4	1	4
Not Hispanic/Latino	20	12	21

Not reported	16	8	17
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Reporting group values	C25 + MTX	Total	
Number of subjects	40	143	
Age Categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	32	114	
From 65-84 years	8	28	
85 years and over	0	1	
Age Continuous Units: years			
arithmetic mean	52.6		
standard deviation	± 13.21	-	
Gender Categorical Units: Subjects			
Female	35	121	
Male	5	22	
Race (NIH/OMB) Units: Subjects			
White	33	115	
Black or African American	0	3	
Asian	4	17	
Other	3	8	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic/Latino	5	14	
Not Hispanic/Latino	17	70	
Not reported	18	59	

End points

End points reporting groups

Reporting group title	PBO + MTX
Reporting group description: Clazakizumab placebo SC every 4 weeks with background methotrexate	
Reporting group title	C1 + MTX
Reporting group description: Clazakizumab 1 mg SC every 4 weeks with background methotrexate	
Reporting group title	C5 + MTX
Reporting group description: Clazakizumab 5 mg SC every 4 weeks with background methotrexate	
Reporting group title	C25 + MTX
Reporting group description: Clazakizumab 25 mg SC every 4 weeks with background methotrexate	
Reporting group title	PBO + MTX
Reporting group description: Clazakizumab placebo SC every 4 weeks with background methotrexate	
Reporting group title	C1 + MTX
Reporting group description: Clazakizumab 1 mg SC every 4 weeks with background methotrexate (n = 20)	
Reporting group title	C5 + MTX
Reporting group description: Clazakizumab 5 mg SC every 4 weeks with background methotrexate	
Reporting group title	C25 + MTX
Reporting group description: Clazakizumab 25 mg SC every 4 weeks with background methotrexate	

Primary: Mean Change from Baseline in Disease Activity Score in 28 joints - C-reactive protein (DAS28-CRP) at Week 12

End point title	Mean Change from Baseline in Disease Activity Score in 28 joints - C-reactive protein (DAS28-CRP) at Week 12
End point description: The DAS using the 28-count subsets of tender/painful joints and swollen joints, together with CRP to derive the DAS28-CRP, was calculated using the following formula: $\text{DAS28-CRP} = 0.56 \cdot \sqrt{\text{TJC28}} + 0.28 \cdot \sqrt{\text{SJC28}} + 0.36 \cdot \ln(\text{CRP} + 1) + 0.014 \cdot \text{GH} + 0.96$; where TJC28 is number of painful joints out of 28 joints, SJC28 is number of swollen joints out of 28 joints, GH is the general health or patients' global assessment of disease activity on a 100 mm VAS, ln is the natural logarithm, and CRP is in mg/L. A score greater than 5.1 implies active disease; less than 3.2, well controlled disease; and less than 2.6, remission.	
End point type	Primary
End point timeframe: Day 1 to Week 12	

End point values	PBO + MTX	C1 + MTX	C5 + MTX	C25 + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	34	15	35	37
Units: Score				
arithmetic mean (standard error)	-0.75 (± 0.2249)	-1.10 (± 0.3303)	-2.10 (± 0.2209)	-2.43 (± 0.2190)

Statistical analyses

Statistical analysis title	P-value of (C1+MTX) vs (PBO +MTX)
Comparison groups	PBO + MTX v C1 + MTX
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3846 ^[1]
Method	Mixed models analysis

Notes:

[1] - Based on the linear mixed model analysis and a hierarchical testing procedure implemented to control the overall type I error rate at 0.05 levels (one-sided)

Statistical analysis title	P-value of (C5+MTX) vs (PBO +MTX)
Comparison groups	PBO + MTX v C5 + MTX
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[2]
Method	Mixed models analysis

Notes:

[2] - Based on the linear mixed model analysis and a hierarchical testing procedure implemented to control the overall type I error rate at 0.05 levels (one-sided)

Statistical analysis title	P-value of (C25+MTX) vs (PBO +MTX)
Comparison groups	PBO + MTX v C25 + MTX
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[3]
Method	Mixed models analysis

Notes:

[3] - Based on the linear mixed model analysis and a hierarchical testing procedure implemented to control the overall type I error rate at 0.05 levels (one-sided)

Secondary: Percentage of Subjects Meeting the Criteria of the American College of Rheumatology for 20%/50%/70% Improvement (ACR 20/50/70) Responses at Week 12

End point title	Percentage of Subjects Meeting the Criteria of the American College of Rheumatology for 20%/50%/70% Improvement (ACR 20/50/70) Responses at Week 12
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End point description:

The ACR x is based on x% improvement (compared with baseline values) in tender and swollen joint counts and on x% improvement in 3 of the remaining 5 core set measures (participant global assessment of pain, participant global assessment of disease activity, physician global assessment of

disease activity, participant assessment of physical function) and 1 acute phase reactant value. x = 20, 50,70 for ACR 20/50/70

End point type	Secondary
End point timeframe:	
Week 12	

End point values	PBO + MTX	C1 + MTX	C5 + MTX	C25 + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	21	42	40
Units: Percentage				
number (confidence interval 95%)				
ACR 20	27.5 (13.7 to 41.3)	14.3 (3.0 to 36.3)	50.0 (34.9 to 65.1)	47.5 (32.0 to 63.0)
ACR 50	7.5 (1.6 to 20.4)	14.3 (3.0 to 36.3)	21.4 (9.0 to 33.8)	22.5 (9.6 to 35.4)
ACR 70	2.5 (0.1 to 13.2)	4.8 (0.1 to 23.8)	9.5 (2.7 to 22.6)	15.0 (3.9 to 26.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Clinical Disease Activity Index (CDAI) Remission Responder (CDAI ≤ 2.8) at Week 12

End point title	Percentage of Subjects with Clinical Disease Activity Index (CDAI) Remission Responder (CDAI ≤ 2.8) at Week 12
End point description:	
Clinical Disease Activity Index (CDAI) is calculated as the simple linear sum of the outcome parameters: tender joint count (TJC) and swollen joint count (SJC) based on a 28-joint assessment, patient global assessment of disease activity (PGA: VAS 0–10 cm), and physician global assessment of disease activity (EGA: VAS 0–10 cm): CDAI = TJC28 + SJC28 + PGA + EGA. CDAI total score=0-76. CDAI ≤2.8 indicates disease remission, >2.8 to 10=low DA, >10 to 22=moderate DA, and >22=high DA. CDAI Remission responder is defined as a CDAI score less than or equal to 2.8.	
End point type	Secondary
End point timeframe:	
At week 12	

End point values	PBO + MTX	C1 + MTX	C5 + MTX	C25 + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	21	42	40
Units: Percentage				
number (confidence interval 95%)	2.5 (0.1 to 13.2)	9.5 (1.2 to 30.4)	9999 (9999 to 9999)	7.5 (1.6 to 20.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Achieved Remission by Criteria of the Simplified Disease Activity Index (SDAI), SDAI ≤ 3.3, at week 12

End point title	Percentage of Subjects Who Achieved Remission by Criteria of the Simplified Disease Activity Index (SDAI), SDAI ≤ 3.3, at week 12
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End point description:

The SDAI is the simple linear sum of 5 outcome parameters: tender joint count (TJC) and swollen joint count (SJC) (based on a 28-joint assessment); patient's and physician's global assessments of disease activity (assessed on 0-10 cm visual analog scale, on which higher scores=greater affection due to disease activity); and C-reactive protein level (mg/dL). SDAI total score=0-86. SDAI ≤3.3 indicates disease remission, >3.4 to 11=low disease activity, >11 to 26=moderate disease activity, and >26=high disease activity. TJC is assessed and recorded at each visit, with no swelling=0, swelling=1. SJC is assessed through identification of joints that are painful under pressure or to passive motion. TJC is recorded on the joint assessment form at each visit, with no tenderness =0, tenderness = 1. Higher score indicates worst health condition.

End point type	Secondary
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End point timeframe:

At week 12

End point values	PBO + MTX	C1 + MTX	C5 + MTX	C25 + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	21	42	40
Units: Percentage				
number (confidence interval 95%)	2.5 (0.1 to 13.2)	9.5 (1.2 to 30.4)	9999 (9999 to 9999)	7.5 (1.6 to 20.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects achieving Boolean Remission (Boolean Remission Rate) at Week 12

End point title	Percentage of Subjects achieving Boolean Remission (Boolean Remission Rate) at Week 12
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End point description:

Remission by Boolean-based definition: Subject must satisfy all of the followings: TJC28 ≤1; SJC28≤1; PGA≤1; CRP≤1 mg/dL where tender joint count (TJC) and swollen joint count (SJC) are based on a 28-joint assessment, patient global assessment of disease activity (PGA: VAS 0–10 cm), physician global assessment of disease activity (EGA: VAS 0–10 cm) and C-reactive protein (CRP in mg/dL). Higher scores indicate worst health condition

End point type	Secondary
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End point timeframe:

Week 12

End point values	PBO + MTX	C1 + MTX	C5 + MTX	C25 + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	21	42	40
Units: Percentage				
number (confidence interval 95%)	5.0 (0.6 to 16.9)	4.8 (0.1 to 23.8)	2.4 (0.1 to 12.6)	5.0 (0.6 to 16.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Health assessment questionnaire disability index (HAQ-DI) change from baseline of at least 0.22 units at Week 12

End point title	Percentage of Subjects with Health assessment questionnaire disability index (HAQ-DI) change from baseline of at least 0.22 units at Week 12
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End point description:

HAQ responder is defined as a reduction of at least 0.22 units from baseline in score on the Health Assessment Questionnaire Disability Index (HAQ-DI), which assesses patients' functional ability by rating their abilities over the previous week. The HAQ-DI includes at least 2 questions from each of 8 categories: dressing and grooming, hygiene, arising, reach, eating, grip, walking, and common daily activities. Patients rate difficulty performing specific tasks: 0=without difficulty, 1=with some difficulty, 2=with much difficulty, and 3=unable to do. The sum of the categories score (the highest scored item in the category) is divided by the number of categories answered, yielding a score from 0-3. When aids, devices, or help is indicated by the patient, the score for the category item is raised from a 0 or a 1 to a 2, but if the patient's highest score for a subcategory is a 3, it stays a 3.

End point type	Secondary
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End point timeframe:

Day 1 to Week 12

End point values	PBO + MTX	C1 + MTX	C5 + MTX	C25 + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	21	42	40
Units: Percentage				
number (confidence interval 95%)	47.5 (32.0 to 63.0)	19.0 (5.4 to 41.9)	47.6 (32.5 to 62.7)	50.0 (34.5 to 65.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With DAS28- Erythrocyte sedimentation rate (ESR) <2.6 at Week 12

End point title	Percentage of Subjects With DAS28- Erythrocyte sedimentation rate (ESR) <2.6 at Week 12
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End point description:

The Disease Activity Score (DAS) using the 28-count subsets of tender/painful joints and swollen joints, together with erythrocyte sedimentation rate ESR, to derive the, DAS28-ESR, was calculated using the

following formula: $\text{DAS28-ESR} = 0.56 \cdot \sqrt{\text{TJC28}} + 0.28 \cdot \sqrt{\text{SJC28}} + 0.70 \cdot \ln(\text{ESR}) + 0.014 \cdot \text{GH}$; where TJC28 is number of painful joints out of 28 joints, SJC28 is number of swollen joints out of 28 joints, GH is the general health or patients' global assessment of disease activity on a 100 mm VAS, ln is the natural logarithm, ESR is in mm/hour. DAS28-ESR scores could range from 0 to 10, where higher scores represented higher disease activity. DAS28-ESR score less than or equal to (\leq) 3.2 indicates LDA, DAS28-ESR score greater than ($>$) 3.2 indicates moderate to high disease activity, and DAS28-ESR less than ($<$) 2.6 indicates remission.

End point type	Secondary
End point timeframe:	
At week 12	

End point values	PBO + MTX	C1 + MTX	C5 + MTX	C25 + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	21	42	40
Units: Percentage				
number (confidence interval 95%)	2.5 (0.1 to 13.2)	4.8 (0.1 to 23.8)	7.1 (1.5 to 19.5)	15.0 (3.9 to 26.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Achieved Remission by Disease Activity Score 28 Based on C-reactive Protein (DAS28-CRP) Criteria, DAS28<2.6, at Week 12

End point title	Percentage of Subjects Who Achieved Remission by Disease Activity Score 28 Based on C-reactive Protein (DAS28-CRP) Criteria, DAS28<2.6, at Week 12
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End point description:

The DAS using the 28-count subsets of tender/painful joints and swollen joints, together with CRP to derive the DAS28-CRP, was calculated using the following formula: $\text{DAS28-CRP} = 0.56 \cdot \sqrt{\text{TJC28}} + 0.28 \cdot \sqrt{\text{SJC28}} + 0.36 \cdot \ln(\text{CRP}+1) + 0.014 \cdot \text{GH} + 0.96$; where TJC28 is number of painful joints out of 28 joints, SJC28 is number of swollen joints out of 28 joints, GH is the general health or patients' global assessment of disease activity on a 100 mm VAS, ln is the natural logarithm, and CRP is in mg/L. A score greater than 5.1 implies active disease; less than 3.2, well controlled disease; and less than 2.6, remission.

End point type	Secondary
End point timeframe:	
At week 12	

End point values	PBO + MTX	C1 + MTX	C5 + MTX	C25 + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	21	42	40
Units: Percentage				
number (confidence interval 95%)	5.0 (0.6 to 16.9)	9.5 (1.2 to 30.4)	14.3 (3.7 to 24.9)	15.0 (3.9 to 26.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Adverse Events

End point title	Number of subjects with Adverse Events
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End point description:

Adverse Events include deaths, serious adverse events, related serious adverse events, discontinuations due to serious adverse events, adverse events, related adverse events and discontinuations due to adverse events

End point type	Secondary
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End point timeframe:

From the 1st dose in DB period up to 150 days post the last dose if subject discontinued study medication or the first dose date in LTE period, whichever is the earlier.

End point values	PBO + MTX	C1 + MTX	C5 + MTX	C25 + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	21	42	40
Units: Subjects				
Deaths	1	0	0	0
Serious Adverse Events (SAEs)	1	0	0	1
Related SAEs	1	0	0	0
Discontinued due to SAEs	0	0	0	0
AEs	14	5	24	28
Related AEs	5	3	9	16
Discontinued due to AEs	0	0	0	1

Statistical analyses

No statistical analyses for this end point

Secondary: Vital Signs - Sitting Systolic Blood Pressure

End point title	Vital Signs - Sitting Systolic Blood Pressure
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End point description:

On each day of study drug administration, vital signs were monitored. Body temperature, blood pressure, respiration rate and heart rate that were taken prior to and after Clazakizumab administration during scheduled visits

End point type	Secondary
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End point timeframe:

Screening Visit 1 to Week 12

End point values	PBO + MTX	C1 + MTX	C5 + MTX	C25 + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	21	42	40
Units: mmHg				
arithmetic mean (standard deviation)				
Screening Visit #1 (N =39,21,42,40)	125.9 (± 14.10)	125.4 (± 15.45)	126.0 (± 12.10)	126.7 (± 16.37)
Screening Visit # 2 (N = 3,3,2, Not reported)	121.3 (± 12.06)	122.0 (± 19.08)	121.5 (± 6.36)	9999 (± 9999)
Day 1 Pre (N = 39, 21, 42, 40)	123.8 (± 12.67)	124.7 (± 15.44)	125.8 (± 12.94)	123.3 (± 13.04)
Day 1 1 Hr Post (N = 38,21,42,40)	123.1 (± 12.36)	121.4 (± 18.56)	123.9 (± 13.86)	119.2 (± 12.62)
Day 1 2 hr Post (N = 39,20,42,40)	124.1 (± 15.24)	124.7 (± 11.49)	123.6 (± 11.75)	120.9 (± 11.87)
Week 1 (N = 40,20,41,40)	123.6 (± 16.54)	124.7 (± 13.89)	126.9 (± 13.56)	125.4 (± 15.25)
Week 2 (N = 40,20,40,40)	122.9 (± 13.08)	121.5 (± 15.81)	121.7 (± 13.28)	124.4 (± 16.25)
Week 4 (N = 38,17,39,38)	122.3 (± 12.27)	122.1 (± 15.27)	127.1 (± 13.31)	123.4 (± 16.25)
Week 8 (N = 34,17,38,37)	123.5 (± 10.66)	121.5 (± 15.26)	127.9 (± 11.48)	128.6 (± 14.80)
Week 12 (N = 27,14,25,27)	123.4 (± 11.75)	123.6 (± 12.31)	128.2 (± 13.65)	127.0 (± 15.38)

Statistical analyses

No statistical analyses for this end point

Secondary: Vital Signs -- Sitting Diastolic Blood Pressure

End point title	Vital Signs -- Sitting Diastolic Blood Pressure
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End point description:

On each day of study drug administration, vital signs were monitored. Body temperature, blood pressure, respiration rate and heart rate that were taken prior to and after Clazakizumab administration during scheduled visits

End point type	Secondary
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End point timeframe:

Screening visit 1 to Week 12

End point values	PBO + MTX	C1 + MTX	C5 + MTX	C25 + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	21	42	40
Units: mmHg				
arithmetic mean (standard deviation)				
Screening visit # 1 (N= 39,21,42,40)	81.3 (± 8.55)	78.7 (± 9.28)	77.5 (± 7.27)	78.4 (± 8.88)
Screening visit # 2 (N = 3, 3,2, not reported)	72.3 (± 9.71)	75.7 (± 4.04)	83.0 (± 1.41)	9999 (± 9999)
Day 1 Pre (N = 39,21,42,40)	77.7 (± 8.02)	74.9 (± 9.37)	78.3 (± 9.23)	76.0 (± 8.13)
Day 1 1 Hr Post (N = 38,21,42,40)	77.0 (± 7.53)	73.5 (± 10.93)	76.3 (± 9.86)	73.0 (± 7.90)
Day 1 2 Hr Post (N = 39,20,42,40)	77.1 (± 8.94)	74.0 (± 7.00)	75.9 (± 8.89)	74.9 (± 6.49)
Week 1 (N = 40,20,41,40)	76.9 (± 8.56)	74.6 (± 9.04)	78.2 (± 8.48)	76.7 (± 9.69)
Week 2 (N = 40,20,40,40)	76.3 (± 7.98)	74.8 (± 10.18)	74.5 (± 8.76)	75.7 (± 10.53)
Week 4 (N = 38, 17, 39, 38)	75.1 (± 9.26)	73.6 (± 7.91)	80.7 (± 8.25)	78.7 (± 10.10)
Week 8 (N = 34,17,38,37)	75.9 (± 8.11)	73.7 (± 10.65)	79.2 (± 8.24)	78.9 (± 9.35)
Week 12 (N = 27,14,25,27)	77.3 (± 7.51)	71.3 (± 5.66)	78.4 (± 9.40)	76.1 (± 9.17)

Statistical analyses

No statistical analyses for this end point

Secondary: Vital Signs -- Sitting Heart Rate

End point title	Vital Signs -- Sitting Heart Rate
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End point description:

On each day of study drug administration, vital signs were monitored. Body temperature, blood pressure, respiration rate and heart rate that were taken prior to and after Clazakizumab administration during scheduled visits

End point type	Secondary
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End point timeframe:

Screening visit 1 to Week 12

End point values	PBO + MTX	C1 + MTX	C5 + MTX	C25 + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	21	42	40
Units: bpm				
arithmetic mean (standard deviation)				
Screening visit #1 (N = 39, 21, 42, 40)	77.6 (± 10.51)	75.0 (± 10.23)	75.2 (± 12.82)	76.6 (± 9.21)
Screening visit #2 (N = 3,3,2, Not reported)	85.7 (± 12.01)	69.3 (± 16.65)	84.0 (± 8.49)	9999 (± 9999)
Day 1 Pre (N = 39,21,42,40)	76.6 (± 10.41)	76.2 (± 9.80)	76.5 (± 9.33)	77.5 (± 10.19)
Day 1 1 Hr Post (N = 38,21,42,40)	74.4 (± 9.99)	74.4 (± 10.61)	77.1 (± 8.58)	75.3 (± 8.92)
Day 1 2 Hr Post (N = 39,20,42,40)	75.7 (± 9.94)	73.3 (± 10.22)	75.6 (± 7.50)	75.9 (± 9.27)
Week 1 (N = 40, 20, 41, 40)	76.8 (± 9.50)	70.9 (± 11.16)	73.6 (± 8.37)	72.0 (± 9.06)
Week 2 (N = 40, 20, 40, 40)	75.9 (± 8.42)	72.7 (± 10.18)	71.9 (± 8.68)	73.7 (± 9.26)
Week 4 (N = 38,17,39,38)	74.7 (± 9.64)	73.8 (± 13.06)	74.9 (± 9.45)	73.3 (± 11.17)
Week 8 (N = 34,17,38,37)	76.0 (± 8.73)	73.0 (± 11.42)	74.1 (± 8.02)	74.4 (± 10.83)
Week 12 (N = 27,14,25,27)	75.1 (± 11.12)	72.7 (± 9.02)	75.0 (± 7.90)	73.9 (± 9.91)

Statistical analyses

No statistical analyses for this end point

Secondary: Vital Signs -- Sitting Respiration rate

End point title	Vital Signs -- Sitting Respiration rate
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End point description:

On each day of study drug administration, vital signs were monitored. Body temperature, blood pressure, respiration rate and heart rate that were taken prior to and after Clazakizumab administration during scheduled visits

End point type	Secondary
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End point timeframe:

Screening visit 1 to Week 12

End point values	PBO + MTX	C1 + MTX	C5 + MTX	C25 + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	21	42	40
Units: per min				
arithmetic mean (standard deviation)				
Screening visit # 1 (N = 38,21,42,40)	16.2 (± 2.45)	15.4 (± 2.42)	16.2 (± 2.22)	16.2 (± 2.03)
Screening visit # 2 (N = 3,3,2, Not reported)	15.0 (± 2.65)	17.7 (± 5.13)	20.0 (± 0.00)	9999 (± 9999)
Day 1 Pre (N = 39,21,41,40)	16.6 (± 2.37)	15.9 (± 2.61)	16.6 (± 2.08)	16.3 (± 2.41)
Day 1 1 Hr Post (N = 38,21,41,40)	16.4 (± 2.56)	15.8 (± 2.11)	16.4 (± 2.15)	16.1 (± 1.94)
Day 1 2 hr Post (N = 39,20,41,40)	16.5 (± 2.45)	15.5 (± 2.35)	16.6 (± 2.27)	16.1 (± 1.95)
Week 1 (N = 40,20,41,40)	16.5 (± 2.21)	16.0 (± 2.36)	16.5 (± 2.28)	15.8 (± 2.80)
Week 2 (N = 40,20,40,40)	16.5 (± 2.52)	15.9 (± 2.20)	16.4 (± 2.35)	16.1 (± 2.37)
Week 4 (N = 38,17,39,38)	16.9 (± 2.50)	16.8 (± 2.88)	16.3 (± 1.89)	16.1 (± 2.41)
Week 8 (N = 34, 17, 38, 37)	16.7 (± 2.40)	16.9 (± 2.99)	16.2 (± 2.03)	16.1 (± 2.21)
Week 12 (N = 27,14, 25 ,27)	17.3 (± 2.14)	16.9 (± 2.54)	16.4 (± 2.06)	16.0 (± 2.18)

Statistical analyses

No statistical analyses for this end point

Secondary: Vital signs -- Sitting temperature

End point title	Vital signs -- Sitting temperature
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End point description:

On each day of study drug administration, vital signs were monitored. Body temperature, blood pressure, respiration rate and heart rate that were taken prior to and after Clazakizumab administration during scheduled visits

End point type	Secondary
End point timeframe:	
Screening visit 1 to Week 12	

End point values	PBO + MTX	C1 + MTX	C5 + MTX	C25 + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	21	42	40
Units: degree C				
arithmetic mean (standard deviation)				
Screening Visit #1 (N = 39,21,42,40)	36.43 (± 0.326)	36.44 (± 0.291)	36.29 (± 0.582)	36.42 (± 0.372)
Screening visit # 2 (N = 3,3,2, Not reported)	36.37 (± 0.115)	36.57 (± 0.252)	36.65 (± 0.071)	9999 (± 9999)
Day 1 Pre (N = 39,21,42,40)	36.47 (± 0.294)	36.49 (± 0.399)	36.36 (± 0.561)	36.27 (± 0.504)
Day 1 1 Hr Post (N = 38,21,42,40)	36.46 (± 0.308)	36.55 (± 0.364)	36.40 (± 0.449)	36.28 (± 0.522)
Day 1 2 Hr Post (N = 39,20,42,40)	36.46 (± 0.264)	36.52 (± 0.341)	36.39 (± 0.524)	36.31 (± 0.402)
Week 1 (N = 40,20,41,40)	36.42 (± 0.365)	36.41 (± 0.380)	36.33 (± 0.420)	36.29 (± 0.498)
Week 2 (N = 40,20,40,40)	36.43 (± 0.387)	36.35 (± 0.389)	36.32 (± 0.533)	36.26 (± 0.546)
Week 4 (N = 38,17,39, 38)	36.37 (± 0.342)	36.46 (± 0.453)	36.31 (± 0.526)	36.26 (± 0.493)
Week 8 (N = 34,17,38,37)	36.44 (± 0.341)	36.35 (± 0.332)	36.32 (± 0.477)	36.36 (± 0.396)
Week 12 (N = 27,14,25,27)	36.52 (± 0.414)	36.36 (± 0.282)	36.38 (± 0.512)	36.36 (± 0.465)

Statistical analyses

No statistical analyses for this end point

Secondary: Marked Laboratory Abnormality -- Hematology I

End point title	Marked Laboratory Abnormality -- Hematology I
End point description:	
ERYTHROCYTE/PLATELET ATTRIBUTES: HEMOGLOBIN HB G/L LOW IF < 80 FOR FEMALES LOW IF < 90 FOR MALES; HIGH IF > 185 FOR BOTH FEMALES AND MALES; PLATELET COUNT PLAT X10*9 C/L LOW IF VALUE < 50	
End point type	Secondary
End point timeframe:	
From 1st dose in double blind period up to 150 days post the last dose if subject discontinued study medication, or the first dose date in LTE period, whichever is the earlier.	

End point values	PBO + MTX	C1 + MTX	C5 + MTX	C25 + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	21	42	40
Units: Percentage				
number (not applicable)				
Hemoglobin Low	0	0	0	0
Hemoglobin High	0	0	0	0
Platelet Count, Low	0	0	0	2.5
Platelet Count, High	9999	9999	9999	9999

Statistical analyses

No statistical analyses for this end point

Secondary: Marked Laboratory Abnormality -- Hematology II

End point title	Marked Laboratory Abnormality -- Hematology II
End point description: QUANTITATIVE WBC:LEUKOCYTES WBC X10*9 C/L LOW IF VALUE < 2.0; WBC DIFFERENTIAL COUNT; NEUTROPHILS (ABSOLUTE) NEUTA X10*9 C/L LOW IF ABSOLUTE COUNT < 1.0; LYMPHOCYTES (ABSOLUTE) LYMPA X10*9 C/L LOW IF ABSOLUTE COUNT < 1.0	
End point type	Secondary
End point timeframe: From the 1st dose in DB period up to 150 days post the last dose if subject discontinued study medication or the first dose date in LTE period, whichever is the earlier.	

End point values	PBO + MTX	C1 + MTX	C5 + MTX	C25 + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	21	42	40
Units: Percentage				
number (not applicable)				
Quant. WBC Leukocytes Low	0	0	0	0
Quant. WBC Leukocytes High	9999	9999	9999	9999
Lymphocytes (Abs.) Low	7.5	5.0	16.7	10.0
Lymphocytes (Abs.) High	9999	9999	9999	9999
Neutrophils (Abs.) Low	0	5.0	0	0
Neutrophils (Abs.) High	9999	9999	9999	9999

Statistical analyses

No statistical analyses for this end point

Secondary: Marked Laboratory Abnormality -- Liver and Kidney Function

End point title	Marked Laboratory Abnormality -- Liver and Kidney Function
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End point description:

LIVER FUNCTION TESTS: ALKALINE PHOSPHATASE (ALP) ALP U/L HIGH IF VALUE > 3X ULN; ASPARTATE AMINOTRANSFERASE (AST) AST U/L HIGH IF VALUE > 5X ULN; ALANINE AMINOTRANSFERASE (ALT) ALT U/L HIGH IF VALUE > 5X ULN; BILIRUBIN, TOTAL TBILI UMOL/L HIGH IF VALUE > 2.0X ULN; BILIRUBIN, DIRECT DBILI UMOL/L HIGH IF VALUE >= 17.1

End point type	Secondary
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End point timeframe:

From the 1st dose in DB period up to 150 days post the last dose if subject discontinued study medication or the first dose date in LTE period, whichever is the earlier.

End point values	PBO + MTX	C1 + MTX	C5 + MTX	C25 + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	21	42	40
Units: Percentage				
number (not applicable)				
Alanine Aminotransferase (ALT) Low	9999	9999	9999	9999
Alanine Aminotransferase (ALT) High	0	0	0	0
Alkaline Phosphatase (ALP) Low	9999	9999	9999	9999
Alkaline Phosphatase (ALP) High	0	0	0	0
Aspartate Aminotransferase (AST) Low	9999	9999	9999	9999
Aspartate Aminotransferase (AST) High	0	0	0	0
Bilirubin, Direct, Low	9999	9999	9999	9999
Bilirubin, Direct, High	0	0	0	0
Bilirubin, Total, Low	9999	9999	9999	9999
Bilirubin, Total, High	0	0	2.4	0

Statistical analyses

No statistical analyses for this end point

Secondary: Marked Laboratory Abnormality -- Other Chemistry Testing

End point title	Marked Laboratory Abnormality -- Other Chemistry Testing
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End point description:

LIPID TESTS: CHOLESTEROL, TOTAL (TC) CHOL MMOL/L HIGH IF VALUE > 10.36; HDL CHOLESTEROL (HDL-C) HDLC MMOL/L LOW IF VALUE < 1.036; LDL CHOLESTEROL (CALCULATED) FASTING LDLF MMOL/L HIGH IF VALUE >= 4.144; TRIGLYCERIDES, FASTING TRIGF MMOL/L HIGH IF VALUE > 5.65; VLDL CHOLESTEROL (VLDL-C) VLDL MMOL/L HIGH IF VALUE >= 1.294

End point type	Secondary
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End point timeframe:

From the 1st dose in DB period up to 150 days post the last dose if subject discontinued study medication or the first dose date in LTE period, whichever is the earlier

End point values	PBO + MTX	C1 + MTX	C5 + MTX	C25 + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	21	42	40
Units: Percentage				
number (not applicable)				
Cholesterol, Total, Low	9999	9999	9999	9999
Cholesterol, Total, High	0	0	0	0
HDL Cholesterol, Low	10.3	21.1	9.5	10.0
HDL, Cholesterol, High	9999	9999	9999	9999
LDL Cholesterol (Calc.) Low	9999	9999	9999	9999
LDL Cholesterol (Calc.) High	10.3	26.3	21.4	27.5
Triglycerides, Fasting, Low	9999	9999	9999	9999
Triglycerides, Fasting, High	0	0	0	0
VLDL Cholesterol, Low	9999	9999	9999	9999
VLDL Cholesterol, High	12.8	15.8	7.1	20.0

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity -- Percentage of Subjects with ADA Positive Response With Respect to Baseline

End point title	Immunogenicity -- Percentage of Subjects with ADA Positive Response With Respect to Baseline
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End point description:

An ADA (anti-drug antibody) positive relative to baseline immunogenicity response using electrochemical luminescence (ECL) assay measurement is defined as: a) A missing baseline immunogenicity measurement and a positive laboratory reported immunogenicity response post-baseline. b) A negative laboratory reported baseline immunogenicity response and a positive laboratory reported immunogenicity response post-baseline. c) A positive laboratory reported baseline immunogenicity response and a positive laboratory reported immunogenicity response post-baseline that has a titer value of 9 folds or greater than the baseline titer value. All other ECL immunogenicity measurements will be classified as negative immunogenicity response.

End point type	Secondary
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End point timeframe:

From the first Clazakizumab dose +1 and up to and including 28 days [represents one dosing interval] after the last dose in the study period

End point values	PBO + MTX	C1 + MTX	C5 + MTX	C25 + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	21	42	40
Units: Percentage				
number (not applicable)				
ADA +ve At Baseline Visit	0	0	0	2.5
ADA +ve (rel. to bsl.) at only 1 On-Trt Visit	0	0	0	0
ADA +ve (rel. to bsl.) at 1 or More On-Trt Visit	0	0	0	0

ADA +ve (rel. to bsl.) at 2 or More On-Trt Visits	0	0	0	0
ADA +ve (rel. to bsl.) at >= 2 Cons. Visits	0	0	0	0
ADA +ve (rel. to bsl.) at 1 Post-Trt Visit	0	0	0	7.1
ADA +ve (rel. to bsl.) at >=2 Post-Trt Visits	0	0	0	0
ADA +ve (rel. to bsl.) at 2 or More Visits	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose of study drug in double blind period to 150 days post the last dose if subject discontinued study medication or the first dose date in long term extension period.

Adverse event reporting additional description:

All SAEs were collected during the screening period and within six months of discontinuation of dosing; Collection of non-serious AE information began at initiation of study drug

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Subjects received placebo matched to clazakizumab subcutaneous (SC) injection once in every four weeks (q4w) for 12 weeks in double-blind period with background of methotrexate.

Reporting group title	Clazakizumab 1 mg
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Reporting group description:

Subjects received 1 milligram (mg) clazakizumab SC injection q4w for 12 weeks in double-blind period and 25 mg clazakizumab SC injection q4w in open-label long term extension period with background of methotrexate.

Reporting group title	Clazakizumab 5 mg
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Reporting group description:

Subjects received 5 mg clazakizumab SC injection q4w for 12 weeks in double-blind period and 25 mg clazakizumab SC injection q4w in open-label long term extension period with background of methotrexate.

Reporting group title	Clazakizumab 25 mg
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Reporting group description:

Subjects received 25 mg clazakizumab SC injection q4w in 12 week double-blind period then in open-label long term extension period with background of methotrexate.

Serious adverse events	Placebo	Clazakizumab 1 mg	Clazakizumab 5 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 40 (5.00%)	0 / 21 (0.00%)	0 / 42 (0.00%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	1	0	0
General disorders and administration site conditions			
Sudden death			
subjects affected / exposed	1 / 40 (2.50%)	0 / 21 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	1 / 40 (2.50%)	0 / 21 (0.00%)	0 / 42 (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
Nausea			
subjects affected / exposed	1 / 40 (2.50%)	0 / 21 (0.00%)	0 / 42 (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
Vomiting			
subjects affected / exposed	1 / 40 (2.50%)	0 / 21 (0.00%)	0 / 42 (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
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	1 / 40 (2.50%)	0 / 21 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 40 (0.00%)	0 / 21 (0.00%)	0 / 42 (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
Viral infection			
subjects affected / exposed	0 / 40 (0.00%)	0 / 21 (0.00%)	0 / 42 (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	Clazakizumab 25 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 40 (5.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Sudden death			

subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	1 / 40 (2.50%)		
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	Clazakizumab 1 mg	Clazakizumab 5 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 40 (35.00%)	6 / 21 (28.57%)	14 / 42 (33.33%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 40 (2.50%)	1 / 21 (4.76%)	2 / 42 (4.76%)
occurrences (all)	1	1	2
Gamma-Glutamyltransferase increased			
subjects affected / exposed	1 / 40 (2.50%)	0 / 21 (0.00%)	1 / 42 (2.38%)
occurrences (all)	1	0	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	3 / 40 (7.50%)	1 / 21 (4.76%)	0 / 42 (0.00%)
occurrences (all)	3	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 40 (5.00%)	0 / 21 (0.00%)	0 / 42 (0.00%)
occurrences (all)	2	0	0
Headache			
subjects affected / exposed	2 / 40 (5.00%)	0 / 21 (0.00%)	0 / 42 (0.00%)
occurrences (all)	2	0	0
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	0 / 40 (0.00%)	0 / 21 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Neutropenia			
subjects affected / exposed	0 / 40 (0.00%)	0 / 21 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	0 / 40 (0.00%)	0 / 21 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Injection site reaction			
subjects affected / exposed	1 / 40 (2.50%)	1 / 21 (4.76%)	2 / 42 (4.76%)
occurrences (all)	1	2	2
Gastrointestinal disorders			

Diarrhoea subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 3	0 / 21 (0.00%) 0	2 / 42 (4.76%) 2
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	0 / 21 (0.00%) 0	1 / 42 (2.38%) 1
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Herpes zoster subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Oral herpes subjects affected / exposed occurrences (all) Sinusitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0 1 / 40 (2.50%) 1 3 / 40 (7.50%) 3 2 / 40 (5.00%) 2 2 / 40 (5.00%) 2 2 / 40 (5.00%) 3 1 / 40 (2.50%) 1	1 / 21 (4.76%) 1 0 / 21 (0.00%) 0 1 / 21 (4.76%) 1 0 / 21 (0.00%) 0 0 / 21 (0.00%) 0 0 / 21 (0.00%) 0 2 / 21 (9.52%) 2 1 / 21 (4.76%) 1	1 / 42 (2.38%) 1 0 / 42 (0.00%) 0 1 / 42 (2.38%) 1 0 / 42 (0.00%) 0 2 / 42 (4.76%) 2 2 / 42 (4.76%) 2 1 / 42 (2.38%) 2
Metabolism and nutrition disorders Dyslipidaemia subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 21 (0.00%) 0	1 / 42 (2.38%) 1

Non-serious adverse events	Clazakizumab 25 mg		
Total subjects affected by non-serious adverse events subjects affected / exposed	15 / 40 (37.50%)		

Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) Gamma-Glutamyltransferase increased subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2 2 / 40 (5.00%) 2		
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1 0 / 40 (0.00%) 0		
Blood and lymphatic system disorders Leukopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 4 4 / 40 (10.00%) 4		
General disorders and administration site conditions Injection site erythema subjects affected / exposed occurrences (all) Injection site reaction subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 5 5 / 40 (12.50%) 7		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		

Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Herpes zoster subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Oral herpes subjects affected / exposed occurrences (all) Sinusitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2 2 / 40 (5.00%) 3 2 / 40 (5.00%) 3 0 / 40 (0.00%) 0 1 / 40 (2.50%) 1 2 / 40 (5.00%) 2 1 / 40 (2.50%) 1		
Metabolism and nutrition disorders Dyslipidaemia subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported