



Clinical trial results:

A Phase IIIb Study to Evaluate the Efficacy, Safety and Tolerability of Subcutaneous (SC) Tocilizumab (TCZ) Given as Monotherapy or in Combination With Methotrexate (MTX) or Other Non Biologics DMARDs in Subjects With Rheumatoid Arthritis

Summary

EudraCT number	2013-002429-52
Trial protocol	ES PT IE
Global end of trial date	09 March 2016

Results information

Result version number	v1 (current)
This version publication date	29 July 2017
First version publication date	29 July 2017

Trial information

Trial identification

Sponsor protocol code	ML28709
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01995201
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH 4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global-roche-genentech-trials@gene.com
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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	09 March 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 July 2015
Global end of trial reached?	Yes
Global end of trial date	09 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of SC TCZ monotherapy or in combination with oral/SC MTX or other non biologic (nb) DMARDs using sustained clinical remission activity (DAS 28-ESR < 2.6) in patients with active RA with inadequate response to nbDMARDs or to one anti-TNF.

Protection of trial subjects:

The study was conducted in full conformance with the ICH E6 guideline for good clinical practices (GCP) and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. The study complied with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). This study was conducted in the European Union (EU)/ European Economic Area, so it complied with the EU Clinical Trial Directive (2001/20/EC), in addition to the local regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 September 2013
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	Ireland: 35
Country: Number of subjects enrolled	Portugal: 39
Country: Number of subjects enrolled	Spain: 327
Worldwide total number of subjects	401
EEA total number of subjects	401

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)	390
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 461 patients were screened and 401 patients were randomized into Phase 1 of the study (from baseline until week 24). A total of 343 patients were randomized into Phase 2 of the study (from week 24 until week 48).

Period 1

Period 1 title	From baseline until week 24
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase 1: Tocilizumab Monotherapy

Arm description:

Participants received Tocilizumab (TCZ), 162mg, by sub-cutaneous injection as a single fixed dose monotherapy once a week for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	RoActemra/Actemra
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

162 mg subcutaneously (SC) qw, Weeks 1-24

Arm title	Phase 1: Combination therapy
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Arm description:

Participants received Tocilizumab (TCZ), 162mg, by sub-cutaneous injection in combination with oral or sub-cutaneous methotrexate (MTX) or other non-biologic Disease Modifying Anti Rheumatic Drugs (nbDMARDs) once a week for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	RoActemra/Actemra
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

162 mg subcutaneously (SC) qw, Weeks 1-24

Investigational medicinal product name	DMARD
Investigational medicinal product code	
Other name	non-biological disease-modifying antirheumatic drugs at stable dose
Pharmaceutical forms	Solution for injection, Tablet
Routes of administration	Oral use, Subcutaneous use

Dosage and administration details:

As per labelling and physician direction

Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection, Tablet
Routes of administration	Oral use, Subcutaneous use

Dosage and administration details:

Stable dose as per labelling and physician direction

Number of subjects in period 1	Phase 1: Tocilizumab Monotherapy	Phase 1: Combination therapy
Started	74	327
Completed	64	281
Not completed	10	46
Adverse event, serious fatal	-	1
Consent withdrawn by subject	2	8
Physician decision	-	2
Anaphylaxis or hypersensitivity reaction	-	3
Adverse event, non-fatal	4	15
Lost to follow-up	2	3
Lack of efficacy	2	5
Protocol deviation	-	9

Period 2

Period 2 title	From week 24 until week 48
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase 2 Arm A1: TCZ +/- nbDMARD once per week (qw)

Arm description:

Participants who achieved sustained clinical remission (DAS28-ESR <2.6) at Week 20 and Week 24 in Part 1 were randomized to tocilizumab given every week monotherapy or in combination with methotrexate or other non-biologics DMARDs from Week 24 to Week 48.

Arm type	Experimental
Investigational medicinal product name	DMARD
Investigational medicinal product code	
Other name	non-biological disease-modifying antirheumatic drugs at stable dose
Pharmaceutical forms	Solution for injection, Tablet
Routes of administration	Oral use, Subcutaneous use

Dosage and administration details:	
As per labelling and physician direction	
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection, Tablet
Routes of administration	Oral use, Subcutaneous use
Dosage and administration details:	
Stable dose as per labelling and physician direction	
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	RoActemra/Actemra
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
162 mg subcutaneously (SC) qw, Weeks 24-48	
Arm title	Phase 2 Arm A2: TCZ +/- nbDMARD every two weeks (q2w)
Arm description:	
Participants who achieved sustained clinical remission (DAS28-ESR <2.6) at Week 20 and Week 24 in Part 1 were randomized to tocilizumab given every 2 weeks monotherapy or in combination with methotrexate or other non-biologics DMARDs from Week 24 to Week 48.	
Arm type	Experimental
Investigational medicinal product name	DMARD
Investigational medicinal product code	
Other name	non-biological disease-modifying antirheumatic drugs at stable dose
Pharmaceutical forms	Solution for injection, Tablet
Routes of administration	Oral use, Subcutaneous use
Dosage and administration details:	
As per labelling and physician direction	
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	RoActemra/Actemra
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
162 mg subcutaneously (SC) q2w, Weeks 24-48	
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection, Tablet
Routes of administration	Oral use, Subcutaneous use
Dosage and administration details:	
Stable dose as per labelling and physician direction	
Arm title	Phase 2 Arm B: Participants With Low Disease Activity
Arm description:	
Participants who did not achieve sustained clinical remission at Week 20 and Week 24 but achieve low disease activity (DAS 28-ESR \leq 3.2) at Week 24 continued with initial treatment of tocilizumab as a single fixed dose monotherapy or in combination with methotrexate or other non-biologics DMARDs from Week 24 to Week 48.	
Arm type	Experimental

Investigational medicinal product name	DMARD
Investigational medicinal product code	
Other name	non-biological disease-modifying antirheumatic drugs at stable dose
Pharmaceutical forms	Solution for injection, Tablet
Routes of administration	Oral use, Subcutaneous use
Dosage and administration details:	
As per labelling and physician direction	
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection, Tablet
Routes of administration	Oral use, Subcutaneous use
Dosage and administration details:	
Stable dose as per labelling and physician direction	
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	RoActemra/Actemra
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
162 mg subcutaneously (SC) qw, Weeks 24-48	
Arm title	Phase 2 Arm C: moderate EULAR response at Week 24
Arm description:	
Patients who achieved moderate EULAR response at Week 24 continued in the study with initial treatment as per investigator's judgement.	
Arm type	Experimental
Investigational medicinal product name	DMARD
Investigational medicinal product code	
Other name	non-biological disease-modifying antirheumatic drugs at stable dose
Pharmaceutical forms	Solution for injection, Tablet
Routes of administration	Oral use, Subcutaneous use
Dosage and administration details:	
As per labelling and physician direction	
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection, Tablet
Routes of administration	Oral use, Subcutaneous use
Dosage and administration details:	
Stable dose as per labelling and physician direction	
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	RoActemra/Actemra
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
162 mg subcutaneously (SC) qw, Weeks 24-48	
Arm title	Phase 2 Arm D: Non responders
Arm description:	
Non responders, safety population.	

Arm type	Experimental
Investigational medicinal product name	DMARD
Investigational medicinal product code	
Other name	non-biological disease-modifying antirheumatic drugs at stable dose
Pharmaceutical forms	Solution for injection, Tablet
Routes of administration	Oral use, Subcutaneous use

Dosage and administration details:

As per labelling and physician direction

Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection, Tablet
Routes of administration	Oral use, Subcutaneous use

Dosage and administration details:

Stable dose as per labelling and physician direction

Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	RoActemra/Actemra
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

162 mg subcutaneously (SC) qw, Weeks 24-48

Number of subjects in period 2 ^[1]	Phase 2 Arm A1: TCZ +/- nbDMARD once per week (qw)	Phase 2 Arm A2: TCZ +/- nbDMARD every two weeks (q2w)	Phase 2 Arm B: Participants With Low Disease Activity
Started	89	90	95
Completed	84	89	89
Not completed	5	1	6
Adverse event, serious fatal	-	-	-
Consent withdrawn by subject	1	-	1
Physician decision	-	-	1
Adverse event, non-fatal	2	1	1
Lost to follow-up	-	-	1
Lack of efficacy	1	-	-
Protocol deviation	1	-	2

Number of subjects in period 2 ^[1]	Phase 2 Arm C: moderate EULAR response at Week 24	Phase 2 Arm D: Non responders
Started	67	2
Completed	59	0
Not completed	8	2
Adverse event, serious fatal	2	-
Consent withdrawn by subject	-	-

Physician decision	-	-
Adverse event, non-fatal	3	1
Lost to follow-up	1	-
Lack of efficacy	2	1
Protocol deviation	-	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Only those patients who achieved sustained clinical remission in Period 1 were admitted in Period 2 of the study.

Baseline characteristics

Reporting groups

Reporting group title	Phase 1: Tocilizumab Monotherapy
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Reporting group description:

Participants received Tocilizumab (TCZ), 162mg, by sub-cutaneous injection as a single fixed dose monotherapy once a week for 24 weeks.

Reporting group title	Phase 1: Combination therapy
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Reporting group description:

Participants received Tocilizumab (TCZ), 162mg, by sub-cutaneous injection in combination with oral or sub-cutaneous methotrexate (MTX) or other non-biologic Disease Modifying Anti Rheumatic Drugs (nbDMARDs) once a week for 24 weeks.

Reporting group values	Phase 1: Tocilizumab Monotherapy	Phase 1: Combination therapy	Total
Number of subjects	74	327	401
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)	58	258	316
From 65-84 years	16	69	85
85 years and over	0	0	0
Female	0	0	0
Male	0	0	0
Age Continuous Units: years			
arithmetic mean	53.5	53.6	
standard deviation	± 12.7	± 12.2	-
Gender, Male/Female Units:			
Male	12	63	75
Female	62	264	326

End points

End points reporting groups

Reporting group title	Phase 1: Tocilizumab Monotherapy
Reporting group description: Participants received Tocilizumab (TCZ), 162mg, by sub-cutaneous injection as a single fixed dose monotherapy once a week for 24 weeks.	
Reporting group title	Phase 1: Combination therapy
Reporting group description: Participants received Tocilizumab (TCZ), 162mg, by sub-cutaneous injection in combination with oral or sub-cutaneous methotrexate (MTX) or other non-biologic Disease Modifying Anti Rheumatic Drugs (nbDMARDs) once a week for 24 weeks.	
Reporting group title	Phase 2 Arm A1: TCZ +/- nbDMARD once per week (qw)
Reporting group description: Participants who achieved sustained clinical remission (DAS28-ESR <2.6) at Week 20 and Week 24 in Part 1 were randomized to tocilizumab given every week monotherapy or in combination with methotrexate or other non-biologics DMARDs from Week 24 to Week 48.	
Reporting group title	Phase 2 Arm A2: TCZ +/- nbDMARD every two weeks (q2w)
Reporting group description: Participants who achieved sustained clinical remission (DAS28-ESR <2.6) at Week 20 and Week 24 in Part 1 were randomized to tocilizumab given every 2 weeks monotherapy or in combination with methotrexate or other non-biologics DMARDs from Week 24 to Week 48.	
Reporting group title	Phase 2 Arm B: Participants With Low Disease Activity
Reporting group description: Participants who did not achieve sustained clinical remission at Week 20 and Week 24 but achieve low disease activity (DAS 28-ESR \leq 3.2) at Week 24 continued with initial treatment of tocilizumab as a single fixed dose monotherapy or in combination with methotrexate or other non-biologics DMARDs from Week 24 to Week 48.	
Reporting group title	Phase 2 Arm C: moderate EULAR response at Week 24
Reporting group description: Patients who achieved moderate EULAR response at Week 24 continued in the study with initial treatment as per investigator's judgement.	
Reporting group title	Phase 2 Arm D: Non responders
Reporting group description: Non responders, safety population.	
Subject analysis set title	Phase 2 Arm A1 - Monotherapy - qw
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants who achieved sustained clinical remission (DAS28-ESR <2.6) at Week 20 and Week 24 in Part 1 were randomized to tocilizumab given every week monotherapy from Week 24 to Week 48.	
Subject analysis set title	Phase 2 Arm A1 - Combination Therapy - qw
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants who achieved sustained clinical remission (DAS28-ESR <2.6) at Week 20 and Week 24 in Part 1 were randomized to tocilizumab given every week in combination with methotrexate or other non-biologics DMARDs from Week 24 to Week 48.	
Subject analysis set title	Phase 2 Arm A2 - Monotherapy - q2w
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants who achieved sustained clinical remission (DAS28-ESR <2.6) at Week 20 and Week 24 in Part 1 were randomized to tocilizumab given every 2 weeks monotherapy from Week 24 to Week 48.	
Subject analysis set title	Phase 2 Arm A2 - Combination Therapy - q2w
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants who achieved sustained clinical remission (DAS28-ESR <2.6) at Week 20 and Week 24 in	

Part 1 were randomized to tocilizumab given every 2 weeks in combination with methotrexate or other non-biologics DMARDs from Week 24 to Week 48.

Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants who received at least one dose of SC TCZ.	

Primary: Percentage of Participants Achieving Sustained Clinical Remission, Disease Activity Scale 28 - Erythrocyte Sedimentation Rate <2.6 (DAS28-ESR <2.6) at Week 20 and Week 24

End point title	Percentage of Participants Achieving Sustained Clinical Remission, Disease Activity Scale 28 - Erythrocyte Sedimentation Rate <2.6 (DAS28-ESR <2.6) at Week 20 and Week 24
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End point description:

The DAS 28 is a combined index for measuring disease activity in RA. The index includes the assessment of 28 joints for swelling and tenderness, acute phase response (ESR or CRP) and general health status. For this study ESR was used to calculate the DAS 28 score. Analyses were conducted on the Full Analysis Set (FAS), i.e. all patients included in the study who received at least one dose of SC Tocilizumab.

End point type	Primary
End point timeframe:	
Week 20 and Week 24	

End point values	Phase 1: Tocilizumab Monotherapy	Phase 1: Combination therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	327		
Units: Percentage of participants				
number (confidence interval 95%)	48.4 (35.75 to 61.27)	52.9 (46.83 to 58.83)		

Statistical analyses

Statistical analysis title	Sustained Clinical Remission
Statistical analysis description:	
Percentage of Participants Achieving Sustained Clinical Remission Disease Activity Scale 28 - Erythrocyte Sedimentation Rate <2.6 (DAS28-ESR <2.6) at Week 20 and Week 24	
Comparison groups	Phase 1: Tocilizumab Monotherapy v Phase 1: Combination therapy
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5231
Method	Chi-squared

Secondary: Mean change in Disease Activity Score 28 - erythrocyte sedimentation

rate (DAS28-ESR)

End point title	Mean change in Disease Activity Score 28 - erythrocyte sedimentation rate (DAS28-ESR)
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End point description:

The DAS 28 is a combined index for measuring disease activity in RA. The index includes the assessment of 28 joints for swelling and tenderness, acute phase response (ESR or CRP) and general health status. For this study ESR was used to calculate the DAS 28 score. Analyses were conducted on the Full Analysis Set (FAS).

End point type	Secondary
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End point timeframe:

From week 24 up to week 48

End point values	Phase 2 Arm A1: TCZ +/- nbDMARD once per week (qw)	Phase 2 Arm A2: TCZ +/- nbDMARD every two weeks (q2w)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	90		
Units: mm/hr				
arithmetic mean (standard deviation)				
Week 24 (n = 89, 90)	-4.07 (± 1.03)	-4.01 (± 1.13)		
Week 28 (n = 87, 88)	-3.94 (± 1.22)	-3.78 (± 1.31)		
Week 32 (n = 86, 90)	-3.97 (± 1.38)	-3.77 (± 1.17)		
Week 36 (n = 86, 88)	-3.82 (± 1.53)	-3.9 (± 1.16)		
Week 40 (n = 84, 88)	-3.95 (± 1.26)	-3.84 (± 1.19)		
Week 44 (n = 82, 88)	-4.05 (± 1.17)	-3.76 (± 1.17)		
Week 48 (n = 82, 88)	-4.14 (± 1.24)	-3.68 (± 1.32)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients allocated in Groups A1 and A2 who remain with clinical remission activity (DAS 28 ESR <2.6) up to Week 48

End point title	Percentage of patients allocated in Groups A1 and A2 who remain with clinical remission activity (DAS 28 ESR <2.6) up to Week 48
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End point description:

The DAS28 is a combined index for measuring disease activity in RA. The index includes the assessment of 28 joints for swelling and tenderness, acute phase response (ESR or CRP), and general health status. For this study ESR will be used to calculate the DAS28 score. Analyses were conducted on the Full Analysis Set (FAS).

End point type	Secondary
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End point timeframe:

From week 28 up to week 48

End point values	Phase 2 Arm A1: TCZ +/- nbDMARD once per week (qw)	Phase 2 Arm A2: TCZ +/- nbDMARD every two weeks (q2w)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	90		
Units: Percentage of participants				
number (confidence interval 95%)				
Week 28 (n = 89, 90)	88.5 (79.88 to 94.35)	84.1 (74.75 to 91.02)		
Week 32 (n = 87, 90)	87.2 (78.27 to 93.44)	81.1 (71.49 to 88.59)		
Week 36 (n = 86, 89)	80.2 (70.25 to 88.04)	86.4 (77.39 to 92.75)		
Week 40 (n = 84, 88)	82.1 (72.26 to 89.65)	80.7 (70.88 to 88.32)		
Week 44 (n = 82, 89)	89 (80.18 to 94.86)	78.4 (68.35 to 86.47)		
Week 48 (n = 84, 89)	91.5 (83.2 to 96.5)	73.9 (63.41 to 82.66)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients reporting change in DAS 28 ESR >1.2 until week 48

End point title	Percentage of patients reporting change in DAS 28 ESR >1.2 until week 48
End point description: The DAS28 is a combined index for measuring disease activity in RA. The index includes the assessment of 28 joints for swelling and tenderness, acute phase response (ESR or CRP), and general health status. For this study ESR will be used to calculate the DAS28 score. Analyses were conducted on the Full Analysis Set (FAS). 000000 to 999999 has been entered as this information is not applicable as the central value is 100%.	
End point type	Secondary
End point timeframe: From week 28 up to week 48	

End point values	Phase 2 Arm A1: TCZ +/- nbDMARD once per week (qw)	Phase 2 Arm A2: TCZ +/- nbDMARD every two weeks (q2w)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	90		
Units: Percentage of participants				
number (confidence interval 95%)				
Week 28 (n = 88, 90)	96.6 (90.25 to 99.28)	96.6 (90.36 to 99.29)		
Week 32 (n = 87, 90)	96.5 (90.14 to 99.27)	95.6 (89.01 to 98.78)		

Week 36 (n = 86, 89)	93 (85.43 to 97.4)	97.7 (92.03 to 99.72)		
Week 40 (n = 84, 88)	98.8 (93.54 to 99.97)	98.9 (93.83 to 99.97)		
Week 44 (n = 82, 89)	98.8 (93.39 to 99.97)	95.5 (88.77 to 98.75)		
Week 48 (n = 84, 89)	100 (0 to 999999)	95.5 (88.77 to 98.75)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with American College of Rheumatology (ACR20, 50, 70, 90) response scores until week 24

End point title	Percentage of patients with American College of Rheumatology (ACR20, 50, 70, 90) response scores until week 24
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End point description:

The definition of improvement of ACR core set of outcome measures includes an improvement equal or higher to the 20%, 50%, 70%, 90% compared to Baseline in both Swollen Joint Count (SJC) and Tender Joint Count (TJC) as well as in three out of five additional parameters: Physician's Global Assessment of disease activity VAS, patient's Global Assessment of disease activity VAS, patient's assessment of pain VAS, HAQ-DI, and acute phase reactant (either CRP or erythrocyte sedimentation rate [ESR]). Analyses were conducted on the Full Analysis Set (FAS).

End point type	Secondary
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End point timeframe:

From week 2 until week 24

End point values	Phase 1: Tocilizumab Monotherapy	Phase 1: Combination therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	319		
Units: Percentage of participants				
number (confidence interval 95%)				
ACR20 - Week 2 (n = 74, 319)	27 (17.35 to 38.61)	31.7 (26.59 to 37.08)		
ACR20 - Week 4 (n = 73, 312)	50.7 (38.72 to 62.6)	49.7 (44 to 55.37)		
ACR20 - Week 8 (n = 73, 300)	67.1 (55.13 to 77.67)	67 (61.36 to 72.3)		
ACR20 - Week 12 (n = 70, 296)	80 (68.73 to 88.61)	74.7 (69.31 to 79.52)		
ACR20 - Week 16 (n = 69, 292)	79.7 (68.31 to 88.44)	75.7 (70.35 to 80.49)		
ACR20 - Week 20 (n = 65, 284)	73.8 (61.46 to 83.97)	81 (75.93 to 85.38)		
ACR20 - Week 24 (n = 64, 281)	79.7 (67.77 to 88.72)	83.3 (78.39 to 87.44)		
ACR20 - LOCF visit (n = 74, 319)	77 (67.77 to 88.72)	79 (78.39 to 87.44)		
ACR50 - Week 2 (n = 74, 319)	9.5 (3.89 to 18.52)	13.2 (9.66 to 17.38)		

ACR50 - Week 4 (n = 73, 312)	20.5 (11.98 to 31.62)	25.3 (20.59 to 30.53)		
ACR50 - Week 8 (n = 73, 300)	37 (25.97 to 49.09)	41.3 (35.7 to 47.14)		
ACR50 - Week 12 (n = 70, 296)	51.4 (39.17 to 63.56)	52.7 (46.84 to 58.51)		
ACR50 - Week 16 (n = 69, 292)	53.6 (41.2 to 65.72)	52.4 (46.5 to 58.25)		
ACR50 - Week 20 (n = 65, 284)	58.5 (45.56 to 70.56)	58.5 (52.48 to 64.24)		
ACR50 - Week 24 (n = 64, 281)	59.4 (46.37 to 71.49)	58.7 (52.72 to 64.53)		
ACR50 - LOCF visit (n = 74, 319)	55.4 (46.37 to 71.49)	54.2 (52.72 to 64.53)		
ACR70 - Week 2 (n = 74, 319)	5.4 (1.49 to 13.27)	2.8 (1.3 to 5.29)		
ACR70 - Week 4 (n = 73, 312)	12.3 (5.8 to 22.12)	10.6 (7.39 to 14.53)		
ACR70 - Week 8 (n = 73, 300)	17.8 (9.84 to 28.53)	22.7 (18.05 to 27.83)		
ACR70 - Week 12 (n = 70, 296)	32.9 (22.09 to 45.12)	27 (22.05 to 32.47)		
ACR70 - Week 16 (n = 69, 292)	29 (18.69 to 41.16)	32.2 (26.87 to 37.88)		
ACR70 - Week 20 (n = 65, 284)	33.8 (22.57 to 46.65)	36.6 (31.01 to 42.52)		
ACR70 - Week 24 (n = 64, 281)	40.6 (28.51 to 53.63)	37.7 (32.03 to 43.67)		
ACR70 - LOCF visit (n = 74, 319)	37.8 (28.51 to 53.63)	33.9 (32.03 to 43.67)		
ACR90 - Week 2 (n = 74, 319)	1.4 (0.03 to 7.3)	0.9 (0.19 to 2.72)		
ACR90 - Week 4 (n = 73, 312)	2.7 (0.33 to 9.55)	1.6 (0.52 to 3.7)		
ACR90 - Week 8 (n = 73, 300)	6.8 (2.26 to 15.26)	7.3 (4.65 to 10.89)		
ACR90 - Week 12 (n = 70, 296)	12.9 (6.05 to 23.01)	8.8 (5.82 to 12.61)		
ACR90 - Week 16 (n = 69, 292)	13 (6.14 to 23.32)	12 (8.49 to 16.27)		
ACR90 - Week 20 (n = 65, 284)	13.8 (6.53 to 24.66)	13.7 (9.95 to 18.29)		
ACR90 - Week 24 (n = 64, 281)	23.4 (13.75 to 35.69)	16.7 (12.56 to 21.61)		
ACR90 - LOCF visit (n = 74, 319)	20.3 (13.75 to 35.69)	15 (12.56 to 21.61)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients With American College of Rheumatology (ACR20, 50, 70, 90) Response Scores Until Week 48

End point title	Percentage of Patients With American College of Rheumatology (ACR20, 50, 70, 90) Response Scores Until Week 48
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End point description:

The definition of improvement of ACR core set of outcome measures includes an improvement equal or higher to the 20%, 50%, 70%, 90% compared to Baseline in both Swollen Joint Count (SJC) and Tender

Joint Count (TJC) as well as in three out of five additional parameters: Physician's Global Assessment of disease activity VAS, patient's Global Assessment of disease activity VAS, patient's assessment of pain VAS, HAQ-DI, and acute phase reactant (either CRP or erythrocyte sedimentation rate [ESR]). Analyses were conducted on the Full Analysis Set (FAS).

End point type	Secondary
End point timeframe:	
From week 28 until week 48	

End point values	Phase 2 Arm A1: TCZ +/- nbDMARD once per week (qw)	Phase 2 Arm A2: TCZ +/- nbDMARD every two weeks (q2w)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	90		
Units: Percentage of participants				
number (confidence interval 95%)				
ARC20 - Week 28 (n = 88, 90)	90 (82.7 to 95.99)	92.2 (84.63 to 96.82)		
ARC20 - Week 32 (n = 87, 90)	93.1 (85.59 to 97.43)	94.4 (87.51 to 98.17)		
ARC20 - Week 36 (n = 86, 89)	84.9 (75.54 to 91.7)	91 (83.05 to 96.04)		
ARC20 - Week 40 (n = 84, 88)	88.1 (79.19 to 94.14)	93.2 (85.75 to 97.46)		
ARC20 - Week 44 (n = 82, 89)	91.5 (83.2 to 96.5)	91 (83.05 to 96.04)		
ARC20 - Week 48 (n = 84, 89)	96.4 (89.92 to 99.26)	88.8 (80.31 to 94.48)		
ARC20 - LOCF visit (n = 89, 90)	95.5 (88.89 to 98.76)	87.8 (79.18 to 93.74)		
ARC50 - Week 28 (n = 88, 90)	79.5 (69.61 to 87.4)	81.1 (71.49 to 88.59)		
ARC50 - Week 32 (n = 87, 90)	85.1 (75.8 to 91.8)	83.3 (74 to 90.36)		
ARC50 - Week 36 (n = 86, 89)	74.4 (63.87 to 83.22)	83.1 (73.73 to 90.25)		
ARC50 - Week 40 (n = 84, 88)	79.8 (69.59 to 87.75)	81.8 (72.16 to 89.24)		
ARC50 - Week 44 (n = 82, 89)	80.5 (70.26 to 88.42)	78.7 (68.69 to 86.63)		
ARC50 - Week 48 (n = 84, 89)	88.1 (79.19 to 94.14)	79.8 (69.93 to 87.55)		
ARC50 - LOCF visit (n = 89, 90)	84.3 (75.02 to 91.12)	78.9 (69.01 to 86.79)		
ARC70 - Week 28 (n = 88, 90)	59.1 (48.09 to 69.46)	57.8 (46.91 to 68.12)		
ARC70 - Week 32 (n = 87, 90)	65.5 (54.56 to 75.39)	54.4 (43.6 to 64.98)		
ARC70 - Week 36 (n = 86, 89)	61.6 (50.51 to 71.92)	62.9 (52.03 to 72.93)		
ARC70 - Week 40 (n = 84, 88)	65.5 (54.31 to 75.52)	59.1 (48.09 to 69.46)		
ARC70 - Week 44 (n = 82, 89)	67.1 (55.81 to 77.06)	59.6 (48.62 to 69.83)		
ARC70 - Week 48 (n = 84, 89)	71.4 (60.53 to 80.76)	65.2 (54.33 to 74.96)		

ARC70 - LOCF visit (n = 89, 90)	68.5 (57.83 to 77.97)	64.4 (53.65 to 74.26)		
ARC90 - Week 28 (n = 88, 90)	27.3 (18.32 to 37.81)	32.2 (22.75 to 42.9)		
ARC90 - Week 32 (n = 87, 90)	35.6 (25.65 to 46.62)	31.1 (21.77 to 41.74)		
ARC90 - Week 36 (n = 86, 89)	33.7 (23.88 to 44.72)	30.3 (21.03 to 40.99)		
ARC90 - Week 40 (n = 84, 88)	41.7 (31 to 52.94)	29.5 (20.29 to 40.22)		
ARC90 - Week 44 (n = 82, 89)	34.1 (24.03 to 45.45)	27 (18.1 to 37.42)		
ARC90 - Week 48 (n = 84, 89)	45.2 (34.34 to 56.48)	32.6 (23.02 to 43.34)		
ARC90 - LOCF visit (n = 89, 90)	42.7 (32.26 to 53.63)	32.2 (22.75 to 42.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with good and moderate clinical response according to European League Against Rheumatism (EULAR) response scores up to week 24

End point title	Number of patients with good and moderate clinical response according to European League Against Rheumatism (EULAR) response scores up to week 24
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End point description:

DAS28-based EULAR response criteria were used to measure individual response as good or moderate depending on the extent of change from baseline and the level of disease activity reached. Good responders: change from baseline >1.2 with $\text{DAS28} \leq 3.2$; moderate responders: change from baseline >1.2 with $\text{DAS28} > 3.2$ to ≤ 5.1 or change from baseline >0.6 to ≤ 1.2 with $\text{DAS28} \leq 5.1$. Analyses were conducted on the Full Analysis Set (FAS).

End point type	Secondary
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End point timeframe:

From week 2 until week 24

End point values	Phase 1: Tocilizumab Monotherapy	Phase 1: Combination therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	327		
Units: Number of participants				
number (not applicable)				
Good response - Week 2 (n = 74, 319)	14	61		
Moderate response - Week 2 (n = 74, 319)	36	196		
Good response - Week 4 (n = 73, 312)	18	109		
Moderate response - Week 4 (n = 73, 312)	49	175		
Good response - Week 8 (n = 73, 300)	37	162		
Moderate response - Week 8 (n = 73, 300)	32	121		

Good response - Week 12 (n = 70, 296)	41	194		
Moderate response - Week 12 (n = 70, 296)	27	95		
Good response - Week 16 (n = 69, 292)	45	209		
Moderate response - Week 16 (n = 69, 292)	22	76		
Good response - Week 20 (n = 65, 284)	45	221		
Moderate response - Week 20 (n = 65, 284)	18	56		
Good response - Week 24 (n = 64, 281)	48	225		
Moderate response - Week 24 (n = 64, 281)	16	53		
Good response - LOCF visit (n = 74, 327)	54	247		
Moderate response - LOCF visit (n = 74, 327)	19	73		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients With Clinical Response According to European League Against Rheumatism (EULAR) Response Scores up to Week 48

End point title	Number of Patients With Clinical Response According to European League Against Rheumatism (EULAR) Response Scores up to Week 48
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End point description:

DAS28-based EULAR response criteria were used to measure individual response as good or moderate depending on the extent of change from baseline and the level of disease activity reached. Good responders: change from baseline >1.2 with $\text{DAS28} \leq 3.2$; moderate responders: change from baseline >1.2 with $\text{DAS28} > 3.2$ to ≤ 5.1 or change from baseline >0.6 to ≤ 1.2 with $\text{DAS28} \leq 5.1$. Analyses were conducted on the Full Analysis Set (FAS).

End point type	Secondary
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End point timeframe:

From week 28 until week 48

End point values	Phase 2 Arm A1: TCZ +/- nbDMARD once per week (qw)	Phase 2 Arm A2: TCZ +/- nbDMARD every two weeks (q2w)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	90		
Units: Number of participants				
number (not applicable)				
Good response - Week 28 (n = 88, 90)	82	77		
Moderate response - Week 28 (n = 88, 90)	5	10		
Good response - Week 32 (n = 87, 90)	79	81		
Moderate response - Week 32 (n = 87, 90)	6	9		
Good response - Week 36 (n = 86, 89)	75	80		

Moderate response - Week 36 (n = 86, 89)	9	8		
Good response - Week 40 (n = 84, 88)	75	81		
Moderate response - Week 40 (n = 84, 88)	9	7		
Good response - Week 44 (n = 82, 89)	78	75		
Moderate response - Week 44 (n = 82, 89)	4	13		
Good response - Week 48 (n = 84, 89)	78	73		
Moderate response - Week 48 (n = 84, 89)	4	15		
Good response - LOCF visit (n = 89, 90)	84	74		
Moderate response - LOCF visit (n = 89, 90)	5	16		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in Clinical Disease Activity Index (CDAI) from baseline up to week 24

End point title	Mean change in Clinical Disease Activity Index (CDAI) from baseline up to week 24
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End point description:

Clinical Disease Activity Index (CDAI) is an index for measuring disease activity in rheumatoid arthritis (RA). The index was calculated using the following formula: CDAI = number of swollen joints using the 28-joint count (SJC28) + number of tender joints using the 28-joint count (TJC28) + patient global assessment of disease (PGA) based on 10 centimeter [cm] Visual Analog Scale [VAS] + physician global assessment of disease (PhGA) based on 10 cm VAS. VAS assessments involved a 10 cm horizontal scale from 0 (no disease activity) to 10 (maximum disease activity). Total CDAI scores ranged from 0 to 76, with higher scores indicating increased disease activity. A negative change from baseline indicates an improvement. Analyses were conducted on the Full Analysis Set (FAS).

End point type	Secondary
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End point timeframe:

From baseline to Week 24

End point values	Phase 1: Tocilizumab Monotherapy	Phase 1: Combination therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	327		
Units: CDAI score				
arithmetic mean (standard deviation)				
Baseline values (n = 74, 327)	33.06 (± 12.45)	32.06 (± 12.28)		
Week 2 (n = 74, 319)	-7.54 (± 9.57)	-8.62 (± 9.22)		
Week 4 (n = 73, 312)	-13.03 (± 10.91)	-13.23 (± 10.65)		
Week 8 (n = 73, 299)	-18.06 (± 11.05)	-18.46 (± 11.61)		
Week 12 (n = 70, 296)	-21.56 (± 11.77)	-20.6 (± 11.42)		

Week 16 (n = 69, 290)	-23.01 (± 12.33)	-21.79 (± 11.57)		
Week 20 (n = 65, 284)	-24.07 (± 11.97)	-22.88 (± 12.1)		
Week 24 (n = 64, 281)	-25.8 (± 13.31)	-23.43 (± 11.62)		
LOCF visit (n = 74, 327)	-24.42 (± 13.5)	-21.58 (± 12.85)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in Clinical Disease Activity Index (CDAI) up to Week 48

End point title	Mean change from baseline in Clinical Disease Activity Index (CDAI) up to Week 48
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End point description:

Clinical Disease Activity Index (CDAI) is an index for measuring disease activity in rheumatoid arthritis (RA). The index was calculated using the following formula: CDAI = number of swollen joints using the 28-joint count (SJC28) + number of tender joints using the 28-joint count (TJC28) + patient global assessment of disease (PGA) based on 10 centimeter [cm] Visual Analog Scale [VAS] + physician global assessment of disease (PhGA) based on 10 cm VAS. VAS assessments involved a 10 cm horizontal scale from 0 (no disease activity) to 10 (maximum disease activity). Total CDAI scores ranged from 0 to 76, with higher scores indicating increased disease activity. A negative change from baseline indicates an improvement. Analyses were conducted on the Full Analysis Set (FAS).

End point type	Secondary
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End point timeframe:

From week 24 until week 48

End point values	Phase 2 Arm A1: TCZ +/- nbDMARD once per week (qw)	Phase 2 Arm A2: TCZ +/- nbDMARD every two weeks (q2w)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	90		
Units: CDAI score				
arithmetic mean (standard deviation)				
Baseline values (n = 89, 90)	29.27 (± 10.9)	29.64 (± 12.13)		
Week 24 (n = 89, 90)	-25.54 (± 10.6)	-25.34 (± 12.1)		
Week 28 (n = 88, 89)	-24.75 (± 10.64)	-24.01 (± 12.3)		
Week 32 (n = 87, 90)	-24.56 (± 12.93)	-25.12 (± 11.64)		
Week 36 (n = 86, 88)	-23.9 (± 11.56)	-25.45 (± 11.42)		
Week 40 (n = 84, 88)	-25.16 (± 10.43)	-25.45 (± 11.75)		
Week 44 (n = 82, 89)	-25.45 (± 10.11)	-25.26 (± 11.75)		

Week 48 (n = 83, 89)	-26.44 (± 11.13)	-25.13 (± 12.51)		
LOCF visit (n = 89, 90)	-25.74 (± 11.29)	-24.87 (± 12.67)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in Simplified Disease Activity Index (SDAI) from baseline up to week 24

End point title	Mean change in Simplified Disease Activity Index (SDAI) from baseline up to week 24
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End point description:

Simplified Disease Activity Index (SDAI) is the numerical sum of five outcome parameters: TJC and SJC (based on a 28-joint assessment), PtGA and PhGA (based on 0-10 cm VAS, where 0 = no disease activity and 10 = worst disease activity), and CRP. SDAI total score ranges from 0 (no disease activity) to 86 (maximal disease activity), where higher scores represents higher disease activity. The SDAI = < 3.3 indicates disease remission, > 3.4 to 11 indicates low disease activity, > 11 to 26 indicates moderate disease activity, and > 26 indicates high disease activity. Analyses were conducted on the Full Analysis Set (FAS).

End point type	Secondary
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End point timeframe:

From baseline to Week 24

End point values	Phase 1: Tocilizumab Monotherapy	Phase 1: Combination therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	327		
Units: SDAI score				
arithmetic mean (standard deviation)				
Baseline values (n = 74, 324)	48.66 (± 31.48)	44.4 (± 22.91)		
Week 2 (n = 72, 309)	-20.45 (± 19.01)	-19.5 (± 18.75)		
Week 4 (n = 70, 308)	-27.86 (± 23.54)	-24.34 (± 20.98)		
Week 8 (n = 72, 292)	-32.61 (± 26.84)	-29.34 (± 21.96)		
Week 12 (n = 70, 291)	-36.23 (± 27.04)	-30.95 (± 23.58)		
Week 16 (n = 69, 286)	-37.82 (± 31.09)	-32.66 (± 22.79)		
Week 20 (n = 64, 277)	-36.79 (± 25.47)	-33.95 (± 23.05)		
Week 24 (n = 63, 277)	-41.38 (± 31.51)	-34.8 (± 22.44)		
LOCF visit (n = 74, 324)	-39.15 (± 30.45)	-32.73 (± 22.84)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in Simplified Disease Activity Index (SDAI) From Week 24 up to Week 48

End point title	Mean Change in Simplified Disease Activity Index (SDAI) From Week 24 up to Week 48
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End point description:

Simplified Disease Activity Index (SDAI) which is the numerical sum of five outcome parameters: TJC and SJC (based on a 28-joint assessment), PtGA and PhGA (based on 0-10 cm VAS, where 0 = no disease activity and 10 = worst disease activity), and CRP. SDAI total score ranges from 0 (no disease activity) to 86 (maximal disease activity), where higher scores represents higher disease activity. The SDAI = < 3.3 indicates disease remission, > 3.4 to 11 indicates low disease activity, > 11 to 26 indicates moderate disease activity, and > 26 indicates high disease activity. Analyses were conducted on the Full Analysis Set (FAS).

End point type	Secondary
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End point timeframe:

From week 24 until week 48

End point values	Phase 2 Arm A1: TCZ +/- nbDMARD once per week (qw)	Phase 2 Arm A2: TCZ +/- nbDMARD every two weeks (q2w)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	90		
Units: SDAI score				
arithmetic mean (standard deviation)				
Baseline values (n = 89, 89)	41.45 (± 24.9)	40.92 (± 21.42)		
Week 24 (n = 88, 90)	-37.02 (± 24.6)	-35.88 (± 20.71)		
Week 28 (n = 86, 87)	-35.15 (± 25.9)	-34.5 (± 20.66)		
Week 32 (n = 86, 90)	-35.6 (± 26.97)	-34.88 (± 20.53)		
Week 36 (n = 86, 88)	-35.29 (± 26.55)	-35.35 (± 20.07)		
Week 40 (n = 83, 88)	-37.26 (± 25.48)	-35.7 (± 19.8)		
Week 44 (n = 82, 89)	-37.09 (± 25.17)	-35.06 (± 21.77)		
Week 48 (n = 82, 88)	-37.93 (± 26.32)	-35.02 (± 21.74)		
LOCF visit (n = 89, 90)	-36.93 (± 25.75)	-34.69 (± 21.75)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in total Tender Joint Counts (TJC) until week 24

End point title	Mean change from baseline in total Tender Joint Counts (TJC) until week 24
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End point description:

TCJ is a clinical assessment of 68 joints which are classified as tender/not tender by pressure and joint manipulation on physical examination. Joint prosthesis, arthrodesis or fused joints are not be taken into consideration. Analyses were conducted on the Full Analysis Set (FAS).

End point type	Secondary
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End point timeframe:

From baseline to Week 24

End point values	Phase 1: Tocilizumab Monotherapy	Phase 1: Combination therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	327		
Units: TJC				
arithmetic mean (standard deviation)				
Baseline visit (n = 74, 327)	18.05 (± 12.98)	19.12 (± 13.38)		
Week 2 (n = 74, 319)	-4.31 (± 7.56)	-5 (± 8.06)		
Week 4 (n = 73, 312)	-7.04 (± 11.77)	-7.96 (± 9.43)		
Week 8 (n = 73, 300)	-9.81 (± 10.37)	-10.9 (± 11.1)		
Week 12 (n = 70, 296)	-12.27 (± 10.47)	-12.01 (± 10.88)		
Week 16 (n = 69, 291)	-13.43 (± 12.35)	-13.09 (± 11.02)		
Week 20 (n = 65, 284)	-13.65 (± 11.73)	-13.7 (± 11.48)		
Week 24 (n = 64, 281)	-15.47 (± 13.35)	-14.2 (± 11.46)		
LOCF visit (n = 74, 327)	-14.36 (± 12.87)	-13.19 (± 11.75)		

Statistical analyses

Secondary: Mean Change From Baseline in Total Tender Joint Counts (TJC) Until Week 48

End point title	Mean Change From Baseline in Total Tender Joint Counts (TJC) Until Week 48
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End point description:

TCJ is a clinical assessment of 68 joints which are classified as tender/not tender by pressure and joint manipulation on physical examination. Joint prosthesis, arthrodesis or fused joints are not be taken into consideration. Analyses were conducted on the Full Analysis Set (FAS).

End point type	Secondary
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End point timeframe:

From week 24 until week 48

End point values	Phase 2 Arm A1: TCZ +/- nbDMARD once per week (qw)	Phase 2 Arm A2: TCZ +/- nbDMARD every two weeks (q2w)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	90		
Units: TJC				
arithmetic mean (standard deviation)				
Baseline values (n = 89, 90)	15.42 (± 9.05)	15.97 (± 12.77)		
Week 28 (n = 88, 90)	-13.66 (± 8.44)	-12.88 (± 11.52)		
Week 32 (n = 87, 90)	-13.4 (± 8.99)	-13.88 (± 11.43)		
Week 36 (n = 86, 89)	-13.13 (± 8.82)	-13.78 (± 11.7)		
Week 40 (n = 84, 88)	-14.06 (± 8.58)	-14.49 (± 12.07)		
Week 44 (n = 82, 89)	-14.32 (± 8.25)	-13.93 (± 11.62)		
Week 48 (n = 84, 89)	-14.4 (± 8.61)	-13.43 (± 12.17)		
LOCF visit (n = 89, 90)	-13.96 (± 8.68)	-13.27 (± 12.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in total Swollen Joint Counts (SJC) from baseline Until Week 24

End point title	Mean Change in total Swollen Joint Counts (SJC) from baseline Until Week 24
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End point description:

SJC is a clinical assessment of 66 joints classified as swollen/not swollen by pressure and joint manipulation on physical examination. Joint prosthesis, arthrodesis or fused joints will not be taken into consideration for swelling. Analyses were conducted on the Full Analysis Set (FAS).

End point type	Secondary
End point timeframe:	
From baseline to Week 24	

End point values	Phase 1: Tocilizumab Monotherapy	Phase 1: Combination therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	327		
Units: SJC				
arithmetic mean (standard deviation)				
Baseline values (n = 74, 327)	10.05 (± 7.99)	9.76 (± 6.64)		
Week 2 (n = 74, 319)	-3.22 (± 4.4)	-3.42 (± 5.1)		
Week 4 (n = 73, 312)	-5.07 (± 5.58)	-5.46 (± 5.41)		
Week 8 (n = 73, 300)	-7.38 (± 6.47)	-6.81 (± 6.03)		
Week 12 (n = 70, 296)	-7.93 (± 7.13)	-7.6 (± 6)		
Week 16 (n = 69, 290)	-8.35 (± 7.71)	-8.01 (± 6.05)		
Week 20 (n = 65, 284)	-8.72 (± 7.56)	-8.37 (± 6.5)		
Week 24 (n = 64, 281)	-9.13 (± 7.66)	-8.38 (± 6.59)		
LOCF visit (n = 74, 327)	-8.47 (± 7.48)	-7.71 (± 6.67)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in Total Swollen Joint Counts (SJC) From Baseline Until Week 48

End point title	Mean Change in Total Swollen Joint Counts (SJC) From Baseline Until Week 48
End point description:	
SJC is a clinical assessment of 66 joints classified as swollen/not swollen by pressure and joint manipulation on physical examination. Joint prosthesis, arthrodesis or fused joints will not be taken into consideration for swelling. Analyses were conducted on the Full Analysis Set (FAS).	
End point type	Secondary
End point timeframe:	
From week 24 until week 48	

End point values	Phase 2 Arm A1: TCZ +/- nbDMARD once per week (qw)	Phase 2 Arm A2: TCZ +/- nbDMARD every two weeks (q2w)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	90		
Units: SJC				
arithmetic mean (standard deviation)				

Baseline values (n = 89, 90)	9.28 (± 6.52)	9.23 (± 7.55)		
Week 28 (n = 88, 90)	-8.64 (± 6.19)	-8.14 (± 6.81)		
Week 32 (n = 87, 90)	-8.54 (± 7.02)	-8.62 (± 7.13)		
Week 36 (n = 86, 89)	-8.48 (± 6.5)	-8.38 (± 6.76)		
Week 40 (n = 84, 88)	-8.85 (± 6.4)	-8.51 (± 6.59)		
Week 44 (n = 82, 89)	-8.73 (± 6.62)	-8.62 (± 6.97)		
Week 48 (n = 84, 89)	-9.06 (± 6.58)	-8.72 (± 7.34)		
LOCF visit (n = 89, 90)	-8.82 (± 6.51)	-8.64 (± 7.33)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentages of patients who achieve DAS28-ESR remission (DAS28 < 2.6) up to Week 48

End point title	Percentages of patients who achieve DAS28-ESR remission (DAS28 < 2.6) up to Week 48
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End point description:

The DAS 28 is a combined index for measuring disease activity in RA. The index includes the assessment of 28 joints for swelling and tenderness, acute phase response (ESR or CRP) and general health status. For this study ESR was used to calculate the DAS 28 score. The CI of 0 to 100 is presented, but is not applicable as the central value is 100%. Analyses were conducted on the Full Analysis Set (FAS).

End point type	Secondary
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End point timeframe:

Week 48

End point values	Phase 2 Arm A1 - Monotherapy - qw	Phase 2 Arm A1 - Combination Therapy - qw	Phase 2 Arm A2 - Monotherapy - q2w	Phase 2 Arm A2 - Combination Therapy - q2w
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	23 ^[1]	66	23	67
Units: Percentage of participants				
arithmetic mean (confidence interval 95%)				
Week 28 (n = 23, 65, 23, 67)	82.6 (61.22 to 95.05)	90.6 (80.7 to 96.48)	87 (66.41 to 97.22)	83.1 (71.73 to 91.24)
Week 32 (n = 22, 65, 23, 67)	81.8 (59.72 to 94.81)	89.1 (78.75 to 95.49)	78.3 (56.3 to 92.54)	82.1 (70.8 to 90.39)
Week 36 (n = 21, 65, 23, 67)	90.5 (69.62 to 98.83)	76.9 (64.81 to 86.47)	86.4 (65.09 to 97.09)	86.4 (75.69 to 93.57)
Week 40 (n = 20, 64, 23, 67)	85 (62.11 to 96.79)	81.3 (69.54 to 89.92)	77.3 (54.63 to 92.18)	81.8 (70.39 to 90.24)
Week 44 (n = 19, 63, 23, 67)	94.7 (73.97 to 99.87)	87.3 (76.5 to 94.35)	77.3 (54.63 to 92.18)	78.8 (66.98 to 87.89)
Week 48 (n = 20, 64, 23, 67)	100 (0 to 100)	89.1 (78.75 to 95.49)	77.3 (54.63 to 92.18)	72.7 (60.36 to 82.97)
LOCF Visit (n = 23, 66, 23, 67)	91.3 (71.96 to 98.93)	89.4 (79.63 to 95.63)	73.9 (51.59 to 89.77)	73.1 (60.9 to 83.24)

Notes:

[1] - 00000 has been entered as this information is not applicable as the central value is 100%.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentages of patients with remission (CDAI<2.8) until week 24

End point title	Percentages of patients with remission (CDAI<2.8) until week 24
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End point description:

Clinical Disease Activity Index (CDAI) is an index for measuring disease activity in rheumatoid arthritis (RA). The index was calculated using the following formula: CDAI = number of swollen joints using the 28-joint count (SJC28) + number of tender joints using the 28-joint count (TJC28) + patient global assessment of disease (PGA) based on 10 centimeter [cm] Visual Analog Scale [VAS] + physician global assessment of disease (PhGA) based on 10 cm VAS. VAS assessments involved a 10 cm horizontal scale from 0 (no disease activity) to 10 (maximum disease activity). Total CDAI scores ranged from 0 to 76, with higher scores indicating increased disease activity. A negative change from baseline indicates an improvement. Analyses were conducted on the Full Analysis Set (FAS).

End point type	Secondary
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End point timeframe:

From baseline to Week 24

End point values	Phase 1: Tocilizumab Monotherapy	Phase 1: Combination therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	327		
Units: Percentage of participants				
number (confidence interval 95%)				
Baseline visit (n = 74, 327)	0 (0 to 0)	0 (0 to 0)		
Week 2 (n = 74, 319)	2.7 (0.33 to 9.42)	1.6 (0.51 to 3.62)		
Week 4 (n = 73, 312)	2.7 (0.33 to 9.55)	5.1 (2.96 to 8.19)		
Week 8 (n = 73, 300)	11 (4.85 to 20.46)	14.4 (10.61 to 18.88)		
Week 12 (n = 70, 296)	15.7 (8.11 to 26.38)	19.3 (14.92 to 24.22)		
Week 16 (n = 69, 292)	18.8 (10.43 to 30.06)	22.8 (18.06 to 28.02)		
Week 20 (n = 65, 284)	27.7 (17.31 to 40.19)	26.8 (21.7 to 32.31)		
Week 24 (n = 64, 281)	29.7 (18.91 to 42.42)	30.2 (24.93 to 35.99)		
LOCF visit (n = 74, 327)	29.7 (19.66 to 41.48)	29.4 (24.48 to 34.62)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentages of Patients With Remission (CDAI<2.8) Until Week 48

End point title	Percentages of Patients With Remission (CDAI<2.8) Until Week 48
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End point description:

Clinical Disease Activity Index (CDAI) is an index for measuring disease activity in rheumatoid arthritis (RA). The index was calculated using the following formula: CDAI = number of swollen joints using the 28-joint count (SJC28) + number of tender joints using the 28-joint count (TJC28) + patient global assessment of disease (PGA) based on 10 centimeter [cm] Visual Analog Scale [VAS] + physician global assessment of disease (PhGA) based on 10 cm VAS. VAS assessments involved a 10 cm horizontal scale from 0 (no disease activity) to 10 (maximum disease activity). Total CDAI scores ranged from 0 to 76, with higher scores indicating increased disease activity. A negative change from baseline indicates an improvement. Analyses were conducted on the Full Analysis Set (FAS).

End point type	Secondary
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End point timeframe:

From week 28 until week 48

End point values	Phase 2 Arm A1: TCZ +/- nbDMARD once per week (qw)	Phase 2 Arm A2: TCZ +/- nbDMARD every two weeks (q2w)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	90		
Units: Percentage of participants				
number (confidence interval 95%)				
Week 28 (n = 88, 90)	46.6 (35.88 to 57.54)	48.3 (37.59 to 59.16)		
Week 32 (n = 87, 90)	48.3 (37.42 to 59.25)	45.6 (35.02 to 56.4)		
Week 36 (n = 86, 89)	52.3 (41.27 to 63.21)	46.6 (35.88 to 57.54)		
Week 40 (n = 84, 88)	52.4 (41.19 to 63.4)	45.5 (34.8 to 56.42)		
Week 44 (n = 82, 89)	50 (38.75 to 61.25)	50.6 (39.75 to 61.33)		
Week 48 (n = 84, 89)	59 (47.69 to 69.72)	53.9 (43.04 to 64.56)		
LOCF Visit (n = 89, 90)	57.8 (46.91 to 68.12)	60.3 (52.77 to 67.56)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentages of Patients With Remission (SDAI<3.3) Until Week 24

End point title	Percentages of Patients With Remission (SDAI<3.3) Until Week 24
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End point description:

Simplified Disease Activity Index (SDAI) is the numerical sum of five outcome parameters: TJC and SJC (based on a 28-joint assessment), PtGA and PhGA (based on 0-10 cm VAS, where 0 = no disease activity and 10 = worst disease activity), and CRP. SDAI total score ranges from 0 (no disease activity) to 86 (maximal disease activity), where higher scores represents higher disease activity. The SDAI = < 3.3 indicates disease remission, > 3.4 to 11 indicates low disease activity, > 11 to 26 indicates moderate disease activity, and > 26 indicates high disease activity. Analyses were conducted on the Full Analysis Set (FAS).

End point type	Secondary
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End point timeframe:

From baseline to Week 24

End point values	Phase 1: Tocilizumab Monotherapy	Phase 1: Combination therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	327		
Units: Percentage of participants				
number (confidence interval 95%)				
Baseline visit (n = 74, 327)	0 (0 to 0)	0 (0 to 0)		
Week 2 (n = 74, 319)	1.4 (0.04 to 7.5)	1.9 (0.71 to 4.14)		
Week 4 (n = 73, 312)	2.9 (0.35 to 9.94)	4.8 (2.72 to 7.83)		
Week 8 (n = 73, 300)	11.1 (4.92 to 20.72)	14.6 (10.75 to 19.13)		
Week 12 (n = 70, 296)	14.3 (7.07 to 24.71)	18.8 (14.47 to 23.72)		
Week 16 (n = 69, 292)	17.4 (9.32 to 28.41)	22.2 (17.56 to 27.47)		
Week 20 (n = 65, 284)	28.1 (17.6 to 40.76)	25.8 (20.77 to 31.36)		
Week 24 (n = 64, 281)	31.7 (20.58 to 44.69)	28.8 (23.53 to 34.49)		
LOCF visit (n = 74, 327)	28.4 (18.5 to 40.05)	25.4 (20.75 to 30.46)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentages of Patients With Remission (SDAI<3.3) Until Week 48

End point title	Percentages of Patients With Remission (SDAI<3.3) Until Week 48
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End point description:

Simplified Disease Activity Index (SDAI) is the numerical sum of five outcome parameters: TJC and SJC (based on a 28-joint assessment), PtGA and PhGA (based on 0-10 cm VAS, where 0 = no disease activity and 10 = worst disease activity), and CRP. SDAI total score ranges from 0 (no disease activity) to 86 (maximal disease activity), where higher scores represents higher disease activity. The SDAI = < 3.3 indicates disease remission, > 3.4 to 11 indicates low disease activity, > 11 to 26 indicates moderate disease activity, and > 26 indicates high disease activity. Analyses were conducted on the Full Analysis Set (FAS).

End point type	Secondary
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End point timeframe:

From week 28 until week 48

End point values	Phase 2 Arm A1: TCZ +/- nbDMARD once per week (qw)	Phase 2 Arm A2: TCZ +/- nbDMARD every two weeks (q2w)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	90		
Units: Percentage of participants				
number (confidence interval 95%)				
Week 28 (n = 88, 90)	50 (39.02 to 60.98)	46 (35.23 to 57)		
Week 32 (n = 87, 90)	48.8 (37.9 to 59.86)	45.6 (35.02 to 56.4)		
Week 36 (n = 86, 89)	53.5 (42.41 to 64.32)	47.7 (36.96 to 58.65)		
Week 40 (n = 84, 88)	55.4 (44.1 to 66.34)	44.3 (33.73 to 55.3)		
Week 44 (n = 82, 89)	50 (38.75 to 61.25)	47.2 (36.51 to 58.06)		
Week 48 (n = 84, 89)	52.4 (41.11 to 63.59)	47.7 (36.96 to 58.65)		
LOCF visit (n = 89, 90)	51.7 (40.48 to 62.41)	47.8 (37.13 to 58.57)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients who achieve low disease activity based on DAS28-ESR criteria (DAS28-ESR ≤ 3.2) up to week 24

End point title	Percentage of patients who achieve low disease activity based on DAS28-ESR criteria (DAS28-ESR ≤ 3.2) up to week 24
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End point description:

The DAS28 is a combined index for measuring disease activity in RA. The index includes the assessment of 28 joints for swelling and tenderness, acute phase response (ESR or CRP), and general health status. For this study ESR is used to calculate the DAS28 score. Analyses were conducted on the Full Analysis Set (FAS).

End point type	Secondary
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End point timeframe:

From baseline to Week 24

End point values	Phase 1: Tocilizumab Monotherapy	Phase 1: Combination therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	327		
Units: Percentage of participants				
number (confidence interval 95%)				
Week 2 (n = 74, 319)	21.6 (12.89 to 32.72)	21.5 (17.12 to 26.47)		
Week 4 (n = 73, 300)	26 (16.45 to 37.62)	36.8 (31.39 to 42.41)		
Week 8 (n = 74, 327)	50.7 (38.72 to 62.6)	55.4 (49.54 to 61.16)		
Week 12 (n = 70, 296)	58.6 (46.17 to 70.23)	67.7 (62.01 to 73)		
Week 16 (n = 69, 292)	66.7 (54.29 to 77.56)	72.4 (66.89 to 77.48)		
Week 20 (n = 65, 284)	67.7 (54.95 to 78.77)	78.2 (72.91 to 82.83)		
Week 24 (n = 64, 281)	75 (62.6 to 84.98)	81.1 (75.98 to 85.49)		
LOCF visit (n = 74, 327)	73 (61.39 to 82.65)	74 (68.9 to 78.68)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients Who Achieve Low Disease Activity Based on DAS28-ESR Criteria (DAS28-ESR \leq 3.2) up to Week 48

End point title	Percentage of Patients Who Achieve Low Disease Activity Based on DAS28-ESR Criteria (DAS28-ESR \leq 3.2) up to Week 48
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End point description:

The DAS28 is a combined index for measuring disease activity in RA. The index includes the assessment of 28 joints for swelling and tenderness, acute phase response (ESR or CRP), and general health status. For this study ESR was used to calculate the DAS28 score. Analyses were conducted on the Full Analysis Set (FAS).

End point type	Secondary
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End point timeframe:

From week 28 until week 48

End point values	Phase 2 Arm A1: TCZ +/- nbDMARD once per week (qw)	Phase 2 Arm A2: TCZ +/- nbDMARD every two weeks (q2w)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	90		
Units: Percentage of participants				
number (confidence interval 95%)				
Week 28 (n = 88, 90)	95.4 (88.64 to 98.73)	88.6 (80.09 to 94.41)		

Week 32 (n = 87, 90)	91.9 (83.95 to 96.66)	92.2 (84.63 to 96.82)		
Week 36 (86, 89)	87.2 (78.27 to 93.44)	92 (84.3 to 96.74)		
Week 40 (n = 84, 88)	89.3 (80.63 to 94.98)	92 (84.3 to 96.74)		
Week 44 (n = 82, 89)	96.3 (89.68 to 99.24)	87.5 (78.73 to 93.59)		
Week 48 (n = 84, 89)	95.1 (87.98 to 98.66)	86.4 (77.39 to 92.75)		
LOCF Visit (n = 89, 90)	94.4 (87.37 to 98.15)	85.6 (76.57 to 92.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients Who Achieve Low Disease Activity Based on CDAI score (CDAI<10) until week 24

End point title	Percentage of Patients Who Achieve Low Disease Activity Based on CDAI score (CDAI<10) until week 24
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End point description:

Clinical Disease Activity Index (CDAI) is an index for measuring disease activity in rheumatoid arthritis (RA). The index was calculated using the following formula: CDAI = number of swollen joints using the 28-joint count (SJC28) + number of tender joints using the 28-joint count (TJC28) + patient global assessment of disease (PGA) based on 10 centimeter [cm] Visual Analog Scale [VAS] + physician global assessment of disease (PhGA) based on 10 cm VAS. VAS assessments involved a 10 cm horizontal scale from 0 (no disease activity) to 10 (maximum disease activity). Total CDAI scores ranged from 0 to 76, with higher scores indicating increased disease activity. A negative change from baseline indicates an improvement. Analyses were conducted on the Full Analysis Set (FAS).

End point type	Secondary
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End point timeframe:

From baseline to Week 24

End point values	Phase 1: Tocilizumab Monotherapy	Phase 1: Combination therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	327		
Units: Percentage of participants				
number (confidence interval 95%)				
Week 2 (n = 74, 319)	13.5 (6.68 to 23.45)	16.9 (12.98 to 21.5)		
Week 4 (n = 73, 312)	24.7 (15.32 to 36.14)	26.9 (22.08 to 32.21)		
Week 8 (n = 73, 300)	41.1 (29.71 to 53.23)	47.5 (41.71 to 53.32)		
Week 12 (n = 70, 296)	57.1 (44.75 to 68.91)	52.4 (46.51 to 58.17)		
Week 16 (n = 69, 292)	62.3 (49.83 to 73.71)	60.7 (54.81 to 66.35)		
Week 20 (n = 65, 284)	66.2 (53.35 to 77.43)	65.1 (59.29 to 70.68)		

Week 24 (n = 64, 281)	71.9 (59.24 to 82.4)	66.9 (61.07 to 72.38)		
LOCF visit (n = 74, 327)	66.2 (54.28 to 76.81)	61.2 (55.64 to 66.48)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients Who Achieve Low Disease Activity Based on CDAI Score (CDAI<10) Until Week 48

End point title	Percentage of Patients Who Achieve Low Disease Activity Based on CDAI Score (CDAI<10) Until Week 48
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End point description:

Clinical Disease Activity Index (CDAI) is an index for measuring disease activity in rheumatoid arthritis (RA). The index was calculated using the following formula: CDAI = number of swollen joints using the 28-joint count (SJC28) + number of tender joints using the 28-joint count (TJC28) + patient global assessment of disease (PGA) based on 10 centimeter [cm] Visual Analog Scale [VAS] + physician global assessment of disease (PhGA) based on 10 cm VAS. VAS assessments involved a 10 cm horizontal scale from 0 (no disease activity) to 10 (maximum disease activity). Total CDAI scores ranged from 0 to 76, with higher scores indicating increased disease activity. A negative change from baseline indicates an improvement. Analyses were conducted on the Full Analysis Set (FAS).

End point type	Secondary
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End point timeframe:

From week 28 until week 48

End point values	Phase 2 Arm A1: TCZ +/- nbDMARD once per week (qw)	Phase 2 Arm A2: TCZ +/- nbDMARD every two weeks (q2w)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	90		
Units: Percentage of participants				
number (confidence interval 95%)				
Week 28 (n = 88, 90)	86.4 (77.39 to 92.75)	85.4 (76.32 to 91.99)		
Week 32 (n = 87, 90)	89.7 (81.27 to 95.16)	86.7 (77.87 to 92.92)		
Week 36 (n = 86, 89)	80.2 (70.25 to 88.04)	89.8 (81.47 to 95.22)		
Week 40 (n = 84, 88)	86.9 (77.78 to 93.28)	88.6 (80.9 to 94.41)		
Week 44 (n = 82, 89)	89 (80.18 to 94.86)	85.4 (76.32 to 91.99)		
Week 48 (n = 84, 89)	92.8 (84.93 to 97.3)	87.6 (78.96 to 93.67)		
LOCF Visit (n = 89, 90)	91 (83.05 to 96.04)	87.8 (79.18 to 93.74)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients who achieved low disease activity (LDA) based on SDAI score (SDAI<11) until week 24

End point title	Percentage of patients who achieved low disease activity (LDA) based on SDAI score (SDAI<11) until week 24
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End point description:

Simplified Disease Activity Index (SDAI) is the numerical sum of five outcome parameters: TJC and SJC (based on a 28-joint assessment), PtGA and PhGA (based on 0-10 cm VAS, where 0 = no disease activity and 10 = worst disease activity), and CRP. SDAI total score ranges from 0 (no disease activity) to 86 (maximal disease activity), where higher scores represents higher disease activity. The SDAI = < 3.3 indicates disease remission, > 3.4 to 11 indicates low disease activity, > 11 to 26 indicates moderate disease activity, and > 26 indicates high disease activity. Analyses were conducted on the Full Analysis Set (FAS).

End point type	Secondary
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End point timeframe:

From baseline to Week 24

End point values	Phase 1: Tocilizumab Monotherapy	Phase 1: Combination therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	327		
Units: Percentage of participants				
number (confidence interval 95%)				
Week 2 (n = 74, 319)	16.7 (8.92 to 27.3)	17.6 (13.56 to 22.32)		
Week 4 (n = 73, 312)	27.1 (17.2 to 39.1)	28.3 (23.36 to 33.65)		
Week 8 (n = 73, 300)	41.7 (30.15 to 53.89)	48.1 (42.31 to 54)		
Week 12 (n = 70, 296)	58.6 (46.17 to 70.23)	55.6 (49.74 to 61.41)		
Week 16 (n = 69, 292)	63.8 (51.31 to 75.01)	62.5 (56.63 to 68.11)		
Week 20 (n = 65, 284)	65.6 (52.7 to 77.05)	66.3 (60.43 to 71.83)		
Week 24 (n = 64, 281)	74.6 (62.06 to 84.73)	67.3 (61.41 to 72.75)		
LOCF visit n = 74, 327)	63.5 (51.51 to 74.4)	56.9 (51.32 to 62.32)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients who achieved low disease activity (LDA) based on SDAI score (SDAI<11) until week 48

End point title	Percentage of patients who achieved low disease activity (LDA) based on SDAI score (SDAI<11) until week 48
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End point description:

Simplified Disease Activity Index (SDAI) is the numerical sum of five outcome parameters: TJC and SJC (based on a 28-joint assessment), PtGA and PhGA (based on 0-10 cm VAS, where 0 = no disease activity and 10 = worst disease activity), and CRP. SDAI total score ranges from 0 (no disease activity) to 86 (maximal disease activity), where higher scores represents higher disease activity. The SDAI = < 3.3 indicates disease remission, > 3.4 to 11 indicates low disease activity, > 11 to 26 indicates moderate disease activity, and > 26 indicates high disease activity. Analyses were conducted on the Full Analysis Set (FAS).

End point type	Secondary
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End point timeframe:

From week 28 until week 48

End point values	Phase 2 Arm A1: TCZ +/- nbDMARD once per week (qw)	Phase 2 Arm A2: TCZ +/- nbDMARD every two weeks (q2w)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	90		
Units: Percentage of participants				
number (confidence interval 95%)				
Week 28 (n = 88, 90)	84.9 (75.54 to 91.7)	83.89 (74.48 to 90.91)		
Week 32 (n = 87, 90)	89.5 (81.06 to 95.1)	85.6 (76.57 to 92.08)		
Week 36 (n = 86, 89)	79.1 (68.95 to 87.1)	87.5 (78.73 to 93.59)		
Week 40 (n = 84, 88)	86.7 (77.52 to 93.19)	86.4 (77.39 to 92.75)		
Week 44 (n = 82, 89)	91.5 (83.2 to 96.5)	82 (72.45 to 89.36)		
Week 48 (n = 84, 89)	93.9 (86.34 to 97.99)	81.8 (72.16 to 89.24)		
LOCF visit (n = 89, 90)	91 (83.05 to 96.04)	81.1 (71.49 to 88.59)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Number of patients reporting adverse events up to week 24

End point title	Safety: Number of patients reporting adverse events up to week 24
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End point description:

Number of patients reporting any treatment emergent adverse event (TEAE), at least one TEAE of special interest, at least one serious TEAE, at least one TEAE leading to dose modification, at least one TEAE leading to discontinuation up to week 24. Analyses were conducted on the Full Analysis Set (FAS).

End point type	Secondary
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End point timeframe:

From baseline to Week 24

End point values	Phase 1: Tocilizumab Monotherapy	Phase 1: Combination therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	327		
Units: Number of participants				
number (not applicable)				
Any treatment emergent adverse event (TEAE)	52	254		
At least one TEAE of special interest	2	13		
At least one serious TEAE	3	10		
At least one TEAE leading to dose modification	24	103		
At least one TEAE leading to discontinuation	4	21		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Number of Patients Reporting Adverse Events up to Week 48

End point title	Safety: Number of Patients Reporting Adverse Events up to Week 48
End point description:	Number of patients reporting any treatment emergent adverse event (TEAE), at least one TEAE of special interest, at least one serious TEAE, at least one TEAE leading to dose modification, at least one TEAE leading to discontinuation up to week 48. Analyses were conducted on the Full Analysis Set (FAS).
End point type	Secondary
End point timeframe:	From week 24 until week 48

End point values	Phase 2 Arm A1: TCZ +/- nbDMARD once per week (qw)	Phase 2 Arm A2: TCZ +/- nbDMARD every two weeks (q2w)	Phase 2 Arm B: Participants With Low Disease Activity	Phase 2 Arm C: moderate EULAR response at Week 24
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	89	90	95	67
Units: Number of participants				
number (not applicable)				
Any TEAE	50	63	68	46
At least one TEAE of special interest	1	2	2	4
At least one serious TEAE	2	1	2	5
At least one TEAE leading to dose modification	15	23	23	21
At least one TEAE leading to discontinuation	0	0	0	2

End point values	Phase 2 Arm D: Non responders			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: Number of participants				
number (not applicable)				
Any TEAE	1			
At least one TEAE of special interest	0			
At least one serious TEAE	1			
At least one TEAE leading to dose modification	1			
At least one TEAE leading to discontinuation	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity: Number of patients with anti-tocilizumab antibodies up to week 24

End point title	Immunogenicity: Number of patients with anti-tocilizumab antibodies up to week 24
End point description:	Number of patients resulting positive to anti-tocilizumab antibodies test are reported. Analyses were conducted on the Full Analysis Set (FAS).
End point type	Secondary
End point timeframe:	From baseline to Week 24

End point values	Phase 1: Tocilizumab Monotherapy	Phase 1: Combination therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	327		
Units: Number of participants				
number (not applicable)				
Screen - Baseline	6	13		
Screen - Week 12	1	2		
Screen - Week 24	3	9		
Confirmatory - Baseline	4	5		
Confirmatory - Week 12	1	0		
Confirmatory - Week 24	1	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity: Number of Patients With Anti-tocilizumab Antibodies up to Week 48

End point title	Immunogenicity: Number of Patients With Anti-tocilizumab Antibodies up to Week 48
End point description: Number of patients resulting positive to anti-tocilizumab antibodies test are reported. Analyses were conducted on the Full Analysis Set (FAS).	
End point type	Secondary
End point timeframe: From week 24 until week 48	

End point values	Phase 2 Arm A1: TCZ +/- nbDMARD once per week (qw)	Phase 2 Arm A2: TCZ +/- nbDMARD every two weeks (q2w)	Phase 2 Arm B: Participants With Low Disease Activity	Phase 2 Arm C: moderate EULAR response at Week 24
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	89	90	95	67
Units: Number of participants				
number (not applicable)				
Screen - Week 36 (n = 86, 89, 91, 59, 0)	0	0	0	2
Screen - Week 48 (n = 84, 89, 89, 59, 0)	1	3	2	3
Confirmatory - Week 36 (n = 86, 89, 88, 59, 0)	0	0	0	1
Confirmatory - Week 48 (n = 84, 89, 88, 59, 0)	0	0	0	1

End point values	Phase 2 Arm D: Non responders			
Subject group type	Reporting group			
Number of subjects analysed	2 ^[2]			
Units: Number of participants				
number (not applicable)				
Screen - Week 36 (n = 86, 89, 91, 59, 0)	11111			
Screen - Week 48 (n = 84, 89, 89, 59, 0)	11111			

Confirmatory - Week 36 (n = 86, 89, 88, 59, 0)	11111			
Confirmatory - Week 48 (n = 84, 89, 88, 59, 0)	11111			

Notes:

[2] - 11111 is not applicable as n = 0.

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity: TCZ levels up to week 24

End point title	Immunogenicity: TCZ levels up to week 24
End point description: Mean concentrations of TCZ in patients' blood are reported. Analyses were conducted on the Full Analysis Set (FAS). 00000 has been entered as this information is not applicable as the analysis was done for one participant only.	
End point type	Secondary
End point timeframe: From baseline to Week 24	

End point values	Phase 1: Tocilizumab Monotherapy	Phase 1: Combination therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	327		
Units: mcg/ml				
arithmetic mean (standard deviation)				
Baseline (n = 1, 4)	0.49 (± 0)	0.67 (± 0.34)		
Week 12 (n = 67, 285)	37.97 (± 20.11)	41.23 (± 20.89)		
Week 24 (n = 62, 273)	46.42 (± 28.35)	46.87 (± 27.65)		

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity: TCZ levels at week 36 and early withdrawal visit

End point title	Immunogenicity: TCZ levels at week 36 and early withdrawal visit
End point description: Mean concentrations of TCZ in patients' blood are reported. Analyses were conducted on the Full Analysis Set (FAS). 00000 has been entered as this information is not applicable as the analysis was done for one participant only. 11111 indicates not applicable as n = 0.	
End point type	Secondary
End point timeframe: Week 36 and early withdrawal visit	

End point values	Phase 2 Arm A1: TCZ +/- nbDMARD once per week (qw)	Phase 2 Arm A2: TCZ +/- nbDMARD every two weeks (q2w)	Phase 2 Arm B: Participants With Low Disease Activity	Phase 2 Arm C: moderate EULAR response at Week 24
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	89	90	95	67
Units: mcg/ml				
arithmetic mean (standard deviation)				
Week 36 (n = 84, 86, 86, 55, 0)	48.47 (± 30.17)	16.77 (± 16.1)	41.89 (± 28.82)	48.33 (± 25.79)
Early withdrawal visit (n = 2, 1, 4, 2, 1)	36.45 (± 18.03)	19.2 (± 0)	24.43 (± 20.83)	13.75 (± 4.6)

End point values	Phase 2 Arm D: Non responders			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: mcg/ml				
arithmetic mean (standard deviation)				
Week 36 (n = 84, 86, 86, 55, 0)	11111 (± 11111)			
Early withdrawal visit (n = 2, 1, 4, 2, 1)	1.78 (± 0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity: SIL-6R Levels up to Week 24

End point title	Immunogenicity: SIL-6R Levels up to Week 24
End point description:	
Mean concentration of SIL-6R in patients' blood are reported. Analyses were conducted on the Full Analysis Set (FAS).	
End point type	Secondary
End point timeframe:	
From baseline to Week 24	

End point values	Phase 1: Tocilizumab Monotherapy	Phase 1: Combination therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	327		
Units: mcg/ml				
arithmetic mean (standard deviation)				
Baseline (n = 74, 321)	42.85 (± 16.26)	39.29 (± 11.1)		
Week 12 (n = 69, 290)	566.47 (± 210.49)	570.34 (± 228.54)		
Week 24 (n = 63, 279)	570.49 (± 198.26)	565.34 (± 198.32)		

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity: SIL-6R Levels at Week 36 and Early Withdrawal Visit

End point title	Immunogenicity: SIL-6R Levels at Week 36 and Early Withdrawal Visit
End point description:	
Mean concentration of SIL-6R in patients' blood are reported. Analyses were conducted on the Full Analysis Set (FAS). 00000 has been entered as this information is not applicable as the analysis was done for one participant only. 11111 indicates not applicable as n = 0.	
End point type	Secondary
End point timeframe:	
Baseline, Week 36 and Early Withdrawal Visit	

End point values	Phase 2 Arm A1: TCZ +/- nbDMARD once per week (qw)	Phase 2 Arm A2: TCZ +/- nbDMARD every two weeks (q2w)	Phase 2 Arm B: Participants With Low Disease Activity	Phase 2 Arm C: moderate EULAR response at Week 24
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	89	90	95	67
Units: mcg/ml				
arithmetic mean (standard deviation)				
Baseline (n = 88, 88, 94, 67, 2)	39.87 (± 10.46)	39.7 (± 16.46)	39.39 (± 11.24)	43.11 (± 11.85)
Week 36 (n = 86, 89, 88, 59, 0)	539.89 (± 152.71)	476.28 (± 156.5)	542.99 (± 168.3)	552.65 (± 184.21)
Early withdrawal visit (n = 3, 1, 6, 5, 1)	412.53 (± 323.49)	643 (± 0)	338.38 (± 230.82)	217.74 (± 236.21)

End point values	Phase 2 Arm D: Non responders			
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Subject group type	Reporting group			
Number of subjects analysed	2			
Units: mcg/ml				
arithmetic mean (standard deviation)				
Baseline (n = 88, 88, 94, 67, 2)	37.3 (± 11.46)			
Week 36 (n = 86, 89, 88, 59, 0)	11111 (± 11111)			
Early withdrawal visit (n = 3, 1, 6, 5, 1)	513 (± 0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Assessment of Disease activity visual analogue scale (VAS) up to Week 24

End point title	Patient Global Assessment of Disease activity visual analogue scale (VAS) up to Week 24
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End point description:

This patient reported outcome assessment represents the patient's overall assessment of their current disease activity on a 100 mm horizontal VAS. The extreme left end of the line should be described as "no disease activity" (symptom-free and no arthritis symptoms) and the extreme right end as "maximum disease activity" (maximum arthritis disease activity). The line was marked by the participant and the distance from the left edge was recorded and the mean values are reported. Analyses were conducted on the Full Analysis Set (FAS).

End point type	Secondary
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End point timeframe:

From baseline to Week 24

End point values	Phase 1: Tocilizumab Monotherapy	Phase 1: Combination therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	327		
Units: Millimeters				
arithmetic mean (standard deviation)				
Baseline (n = 74, 319)	65.26 (± 19.77)	59.4 (± 17.61)		
Week 2 (n = 74, 319)	49.53 (± 22.78)	44.16 (± 21.97)		
Week 4 (n = 73, 312)	38.21 (± 22.92)	35.19 (± 20.83)		
Week 8 (n = 73, 300)	30.03 (± 21.65)	26.04 (± 20.59)		
Week 12 (n = 70, 296)	22.71 (± 18.56)	22.24 (± 17.97)		
Week 16 (n = 69, 291)	19.28 (± 18.22)	20.71 (± 18.65)		
Week 20 (n = 65, 284)	16.8 (± 16.68)	18.79 (± 17.79)		
Week 24 (n = 64, 281)	16.63 (± 15.19)	19 (± 18.36)		

LOCF visit (n = 74, 327)	20.36 (± 19.25)	22.23 (± 20.86)		
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Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Assessment of Disease Activity Visual Analogue Scale (VAS) up to Week 48

End point title	Patient Global Assessment of Disease Activity Visual Analogue Scale (VAS) up to Week 48
End point description: This patient reported outcome assessment represents the patient's overall assessment of their current disease activity on a 100 mm horizontal VAS. The extreme left end of the line should be described as "no disease activity" (symptom-free and no arthritis symptoms) and the extreme right end as "maximum disease activity" (maximum arthritis disease activity). The line was marked by the participant and the distance from the left edge was recorded and the mean values are reported. Analyses were conducted on the Full Analysis Set (FAS).	
End point type	Secondary
End point timeframe: Baseline, from week 28 until week 48	

End point values	Phase 2 Arm A1: TCZ +/- nbDMARD once per week (qw)	Phase 2 Arm A2: TCZ +/- nbDMARD every two weeks (q2w)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	90		
Units: Millimeters				
arithmetic mean (standard deviation)				
Baseline (n = 89, 90)	58.97 (± 17.4)	60.96 (± 20.13)		
Week 28 (n = 88, 90)	11.97 (± 14.1)	12.74 (± 15.07)		
Week 32 (n = 87, 90)	10.78 (± 15.33)	10.8 (± 11.36)		
Week 36 (n = 86, 89)	11.99 (± 16.23)	10.3 (± 13.2)		
Week 40 (n = 84, 88)	10.62 (± 13.49)	10.94 (± 14.12)		
Week 44 (n = 82, 89)	9.5 (± 11.3)	10.06 (± 12.14)		
Week 48 (n = 84, 89)	8.13 (± 10.52)	9.99 (± 13.88)		
LOCF visit (n = 89, 90)	8.97 (± 11.63)	10.21 (± 13.96)		

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of pain reported by the patient (VAS) until week 24

End point title	Assessment of pain reported by the patient (VAS) until week 24
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End point description:

This patient reported outcome assessment represents the patient's assessment of his/her current level of pain on a 100 mm horizontal VAS. The extreme left end of the line should be described as "no pain" and the extreme right end as "unbearable pain". Analyses were conducted on the Full Analysis Set (FAS).

End point type	Secondary
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End point timeframe:

From baseline to Week 24

End point values	Phase 1: Tocilizumab Monotherapy	Phase 1: Combination therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	327		
Units: Millimeters				
arithmetic mean (standard deviation)				
Baseline (n = 74, 327)	66.38 (± 20.7)	58.59 (± 23.7)		
Week 2 (n = 74, 319)	53.2 (± 24.43)	47.46 (± 25.14)		
Week 4 (n = 73, 312)	43.11 (± 24.69)	42.88 (± 24.57)		
Week 8 (n = 73, 300)	35.95 (± 24.62)	34.28 (± 25.94)		
Week 12 (n = 70, 296)	29.44 (± 22.37)	31.07 (± 24.97)		
Week 16 (n = 69, 292)	32.17 (± 22.01)	30.18 (± 24)		
Week 20 (n = 65, 284)	26.58 (± 22.13)	28.26 (± 24.16)		
Week 24 (n = 64, 281)	23.56 (± 21.17)	26.43 (± 23.3)		
LOCF visit (n = 74, 327)	27.34 (± 24.41)	29.78 (± 25.18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of Pain Reported by the Patient (VAS) Until Week 48

End point title	Assessment of Pain Reported by the Patient (VAS) Until Week 48
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End point description:

This patient reported outcome assessment represents the patient's assessment of his/her current level of pain on a 100 mm horizontal VAS. The extreme left end of the line should be described as "no pain" and the extreme right end as "unbearable pain". Analyses were conducted on the Full Analysis Set (FAS).

End point type	Secondary
End point timeframe:	
Baseline, from week 28 until week 48	

End point values	Phase 2 Arm A1: TCZ +/- nbDMARD once per week (qw)	Phase 2 Arm A2: TCZ +/- nbDMARD every two weeks (q2w)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	90		
Units: Millimeters				
arithmetic mean (standard deviation)				
Baseline (n = 89, 90)	55.73 (± 21.68)	56 (± 23.56)		
Week 28 (n = 88, 90)	17.33 (± 20.14)	15.67 (± 17.65)		
Week 32 (n = 87, 90)	17.08 (± 20.47)	17.27 (± 17.69)		
Week 36 (n = 86, 88)	18.81 (± 23.88)	14.36 (± 15.65)		
Week 40 (n = 84, 88)	16.96 (± 20.89)	17.07 (± 17.86)		
Week 44 (n = 82, 89)	15.05 (± 18.02)	16.27 (± 17.7)		
Week 48 (n = 84, 89)	11.9 (± 15.56)	16.31 (± 19.85)		
LOCF visit (n = 89, 90)	12.74 (± 15.99)	16.41 (± 19.76)		

Statistical analyses

No statistical analyses for this end point

Secondary: Health Assessment Questionnaire-Disability Index (HAQ-DI) up to Week 24

End point title	Health Assessment Questionnaire-Disability Index (HAQ-DI) up to Week 24
End point description:	
<p>The Stanford HAQ-DI is a patient-oriented outcome assessment questionnaire specific for RA. It consists of 20 questions referring to eight component sets: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities. To respond to each question, a four-level response (score of 0 to 3 points), with higher scores showing larger functional limitations, was chosen. Scoring was as follows with respect to performance of participant's everyday activities: 0 (equals)=without difficulties; 1=with some difficulties; 2=with great difficulties; and 3=unable to perform these actions at all. Minimum score was 0, maximum score was 3. Analyses were conducted on the Full Analysis Set (FAS).</p>	
End point type	Secondary
End point timeframe:	
From baseline to Week 24	

End point values	Phase 1: Tocilizumab Monotherapy	Phase 1: Combination therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	327		
Units: HAQ-DI score				
arithmetic mean (standard deviation)				
Baseline (n = 74, 324)	1.49 (± 0.76)	1.36 (± 0.7)		
Week 2 (n = 73, 317)	1.39 (± 0.74)	1.18 (± 0.69)		
Week 4 (n = 72, 309)	1.2 (± 0.74)	1.05 (± 0.69)		
Week 8 (n = 73, 300)	1.1 (± 0.75)	0.95 (± 0.71)		
Week 12 (n = 69, 295)	0.99 (± 0.74)	0.91 (± 0.71)		
Week 16 (n = 69, 292)	0.99 (± 0.72)	0.87 (± 0.7)		
Week 20 (n = 65, 283)	0.88 (± 0.7)	0.83 (± 0.71)		
Week 24 (n = 63, 281)	0.85 (± 0.71)	0.82 (± 0.7)		
LOCF visit (n = 74, 327)	0.97 (± 0.76)	0.88 (± 0.73)		

Statistical analyses

No statistical analyses for this end point

Secondary: Health Assessment Questionnaire-Disability Index (HAQ-DI) up to Week 48

End point title	Health Assessment Questionnaire-Disability Index (HAQ-DI) up to Week 48
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End point description:

The Stanford HAQ-DI is a patient-oriented outcome assessment questionnaire specific for RA. It consists of 20 questions referring to eight component sets: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities. To respond to each question, a four-level response (score of 0 to 3 points), with higher scores showing larger functional limitations, was chosen. Scoring was as follows with respect to performance of participant's everyday activities: 0 (equals)=without difficulties; 1=with some difficulties; 2=with great difficulties; and 3=unable to perform these actions at all. Minimum score was 0, maximum score was 3. Analyses were conducted on the Full Analysis Set (FAS).

End point type	Secondary
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End point timeframe:

Baseline, from week 28 until week 48

End point values	Phase 2 Arm A1: TCZ +/- nbDMARD once per week (qw)	Phase 2 Arm A2: TCZ +/- nbDMARD every two weeks (q2w)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	90		
Units: HAQ-DI score				
arithmetic mean (standard deviation)				

Baseline (n = 88, 89)	1.21 (± 0.68)	1.2 (± 0.7)		
Week 28 (n = 88, 90)	0.58 (± 0.56)	0.57 (± 0.64)		
Week 32 (n = 87, 90)	0.55 (± 0.58)	0.57 (± 0.63)		
Week 36 (n = 86, 88)	0.6 (± 0.6)	0.56 (± 0.64)		
Week 40 (n = 84, 88)	0.55 (± 0.56)	0.61 (± 0.67)		
Week 44 (n = 82, 89)	0.53 (± 0.57)	0.58 (± 0.66)		
Week 48 (n = 84, 89)	0.53 (± 0.61)	0.57 (± 0.66)		
LOCF visit (n = 89, 90)	0.55 (± 0.61)	0.56 (± 0.66)		

Statistical analyses

No statistical analyses for this end point

Secondary: Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) up to Week 24

End point title	Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) up to Week 24
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End point description:

The symptom-specific measure FACIT-F assesses chronic illness therapy with special emphasis on fatigue in the past 7 days and consists of 5 dimensions: 1) physical well-being, 2) social/family well-being, 3) emotional well-being, 4) functional well-being, and 5) additional concerns. Each of the questions is categorically answered using the scales 0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, and 4=very much for a total possible FACIT-F score of 0 to 160. The figures are reversed during score calculations, so that higher score values indicate more favorable conditions. Analyses were conducted on the Full Analysis Set (FAS).

End point type	Secondary
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End point timeframe:

From baseline to Week 24

End point values	Phase 1: Tocilizumab Monotherapy	Phase 1: Combination therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	327		
Units: FACIT-F score				
arithmetic mean (standard deviation)				
Baseline (n = 74, 327)	81.72 (± 24.75)	89.16 (± 24.49)		
Week 2 (n = 74, 319)	86.64 (± 25)	95.82 (± 25.42)		
Week 4 (n = 73, 312)	92.26 (± 25.3)	99.54 (± 27.15)		
Week 8 (n = 73, 300)	96.45 (± 25.88)	103.46 (± 27.25)		
Week 12 (n = 70, 296)	98.29 (± 25.47)	104.08 (± 26.79)		
Week 16 (n = 69, 292)	98.41 (± 27.08)	105.51 (± 26.94)		
Week 20 (n = 65, 284)	102.46 (± 27.24)	104.91 (± 27.47)		
Week 24 (n = 64, 281)	104.36 (± 27.16)	107.01 (± 27.6)		

LOCF visit (n = 74, 327)	101.38 (± 28.24)	104.65 (± 28.07)		
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Statistical analyses

No statistical analyses for this end point

Secondary: Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) up to Week 48

End point title	Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) up to Week 48
End point description: The symptom-specific measure FACIT-F assesses chronic illness therapy with special emphasis on fatigue in the past 7 days and consists of 5 dimensions: 1) physical well-being, 2) social/family well-being, 3) emotional well-being, 4) functional well-being, and 5) additional concerns. Each of the questions is categorically answered using the scales 0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, and 4=very much for a total possible FACIT-F score of 0 to 160. The figures are reversed during score calculations, so that higher score values indicate more favorable conditions. Analyses were conducted on the Full Analysis Set (FAS).	
End point type	Secondary
End point timeframe: Baseline, from week 28 until week 48	

End point values	Phase 2 Arm A1: TCZ +/- nbDMARD once per week (qw)	Phase 2 Arm A2: TCZ +/- nbDMARD every two weeks (q2w)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	90		
Units: FACIT-F score				
arithmetic mean (standard deviation)				
Baseline (n = 89, 90)	17.36 (± 5.16)	17.13 (± 5.67)		
Week 28 (n = 88, 90)	23.5 (± 3.82)	23.12 (± 4.47)		
Week 32 (n = 87, 90)	23.62 (± 4.16)	22.98 (± 4.86)		
Week 36 (n = 86, 88)	23.23 (± 4.21)	22.9 (± 4.64)		
Week 40 (n = 84, 88)	23.39 (± 4.4)	23.02 (± 4.38)		
Week 44 (n = 82, 89)	23.48 (± 4.21)	23.13 (± 4.45)		
Week 48 (n = 84, 89)	23.95 (± 3.79)	22.87 (± 4.87)		
LOCF visit (n = 89, 90)	23.69 (± 4.07)	22.88 (± 4.85)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

After initiation of study drug, all AEs, regardless of relationship to study drug, are reported until study closure.

Adverse event reporting additional description:

In this section the arms are not mutually exclusive because they report AE data across two different phases of the study. In Non Serious Adverse events section data was calculated separately according to the two different phases of the study, i.e. Phase 1 mono-therapy and Phase 1 combination therapy groups, and the Phase 2 groups.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	Phase 1: Tocilizumab Monotherapy
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Reporting group description:

Participants received Tocilizumab (TCZ), 162mg, by sub-cutaneous injection as a single fixed dose monotherapy once a week for 24 weeks.

Reporting group title	Phase 1: Combination therapy
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Reporting group description:

Participants received Tocilizumab (TCZ), 162mg, by sub-cutaneous injection in combination with oral or sub-cutaneous methotrexate (MTX) or other non-biologic Disease Modifying Anti Rheumatic Drugs (nbDMARDs) once a week for 24 weeks.

Reporting group title	Phase 2 Arm A2: TCZ +/- nbDMARD every two weeks (q2w)
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Reporting group description:

Participants who achieved sustained clinical remission (DAS28-ESR <2.6) at Week 20 and Week 24 in Part 1 were randomized to tocilizumab given every 2 weeks monotherapy or in combination with methotrexate or other non-biologics DMARDs from Week 24 to Week 48.

Reporting group title	Phase 2 Arm A1: TCZ +/- nbDMARD once per week (qw)
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Reporting group description:

Participants who achieved sustained clinical remission (DAS28-ESR <2.6) at Week 20 and Week 24 in Part 1 were randomized to tocilizumab given every week monotherapy or in combination with methotrexate or other non-biologics DMARDs from Week 24 to Week 48.

Reporting group title	Phase 2 Arm B: Participants With Low Disease Activity
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Reporting group description:

Participants who did not achieve sustained clinical remission at Week 20 and Week 24 but achieve low disease activity (DAS 28-ESR \leq 3.2) at Week 24 continued with initial treatment of tocilizumab as a single fixed dose monotherapy or in combination with methotrexate or other non-biologics DMARDs from Week 24 to Week 48.

Reporting group title	Phase 2 Arm D: Non responders
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Reporting group description:

Patients who didn't achieve any therapeutic response up to week 24 and were discontinued from the study.

Reporting group title	Phase 2 Arm C: moderate EULAR response at Week 24
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Reporting group description:

Patients who achieved moderate EULAR response at Week 24 continued in the study with initial treatment as per investigator's judgement.

Serious adverse events	Phase 1: Tocilizumab Monotherapy	Phase 1: Combination therapy	Phase 2 Arm A2: TCZ +/- nbDMARD every two weeks (q2w)
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 74 (4.05%)	10 / 327 (3.06%)	1 / 90 (1.11%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastatic malignant melanoma			
subjects affected / exposed	0 / 74 (0.00%)	0 / 327 (0.00%)	0 / 90 (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
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 74 (0.00%)	1 / 327 (0.31%)	0 / 90 (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
Urinary tract neoplasm			
subjects affected / exposed	0 / 74 (0.00%)	1 / 327 (0.31%)	0 / 90 (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
Injury, poisoning and procedural complications			
Spinal fracture			
subjects affected / exposed	0 / 74 (0.00%)	0 / 327 (0.00%)	0 / 90 (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			
Deep vein thrombosis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 327 (0.00%)	0 / 90 (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
Thrombophlebitis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 327 (0.31%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			

subjects affected / exposed	0 / 74 (0.00%)	0 / 327 (0.00%)	0 / 90 (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
Cardiac disorders			
Pericarditis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 327 (0.00%)	0 / 90 (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
Acute coronary syndrome			
subjects affected / exposed	0 / 74 (0.00%)	0 / 327 (0.00%)	0 / 90 (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
Coronary artery disease			
subjects affected / exposed	0 / 74 (0.00%)	0 / 327 (0.00%)	0 / 90 (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
Myocardial infarction			
subjects affected / exposed	0 / 74 (0.00%)	0 / 327 (0.00%)	0 / 90 (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
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 74 (1.35%)	0 / 327 (0.00%)	0 / 90 (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
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 74 (0.00%)	1 / 327 (0.31%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Duodenal perforation			

subjects affected / exposed	0 / 74 (0.00%)	1 / 327 (0.31%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 74 (0.00%)	1 / 327 (0.31%)	0 / 90 (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
Ascites			
subjects affected / exposed	0 / 74 (0.00%)	0 / 327 (0.00%)	0 / 90 (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
Diverticular perforation			
subjects affected / exposed	0 / 74 (0.00%)	0 / 327 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 74 (0.00%)	0 / 327 (0.00%)	0 / 90 (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
Hepatobiliary disorders			
Biliary fistula			
subjects affected / exposed	0 / 74 (0.00%)	1 / 327 (0.31%)	0 / 90 (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
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease			
subjects affected / exposed	0 / 74 (0.00%)	1 / 327 (0.31%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 74 (0.00%)	2 / 327 (0.61%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 327 (0.00%)	0 / 90 (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
Back pain			
subjects affected / exposed	0 / 74 (0.00%)	1 / 327 (0.31%)	0 / 90 (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			
Breast abscess			
subjects affected / exposed	0 / 74 (0.00%)	0 / 327 (0.00%)	0 / 90 (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
Abscess limb			
subjects affected / exposed	0 / 74 (0.00%)	1 / 327 (0.31%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 74 (0.00%)	2 / 327 (0.61%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 74 (0.00%)	1 / 327 (0.31%)	0 / 90 (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

Serious adverse events	Phase 2 Arm A1: TCZ +/- nbDMARD once per week (qw)	Phase 2 Arm B: Participants With Low Disease Activity	Phase 2 Arm D: Non responders
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 89 (2.25%)	2 / 95 (2.11%)	1 / 2 (50.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastatic malignant melanoma			

subjects affected / exposed	1 / 89 (1.12%)	0 / 95 (0.00%)	0 / 2 (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
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 89 (0.00%)	0 / 95 (0.00%)	0 / 2 (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
Urinary tract neoplasm			
subjects affected / exposed	0 / 89 (0.00%)	0 / 95 (0.00%)	0 / 2 (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
Injury, poisoning and procedural complications			
Spinal fracture			
subjects affected / exposed	0 / 89 (0.00%)	0 / 95 (0.00%)	0 / 2 (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			
Deep vein thrombosis			
subjects affected / exposed	0 / 89 (0.00%)	0 / 95 (0.00%)	0 / 2 (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
Thrombophlebitis			
subjects affected / exposed	0 / 89 (0.00%)	0 / 95 (0.00%)	0 / 2 (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
Hypertensive crisis			
subjects affected / exposed	0 / 89 (0.00%)	0 / 95 (0.00%)	0 / 2 (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
Cardiac disorders			
Pericarditis			
subjects affected / exposed	0 / 89 (0.00%)	0 / 95 (0.00%)	0 / 2 (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

Acute coronary syndrome			
subjects affected / exposed	0 / 89 (0.00%)	1 / 95 (1.05%)	0 / 2 (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
Coronary artery disease			
subjects affected / exposed	0 / 89 (0.00%)	0 / 95 (0.00%)	0 / 2 (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
Myocardial infarction			
subjects affected / exposed	0 / 89 (0.00%)	0 / 95 (0.00%)	0 / 2 (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
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 89 (0.00%)	0 / 95 (0.00%)	0 / 2 (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
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 89 (0.00%)	0 / 95 (0.00%)	0 / 2 (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			
Duodenal perforation			
subjects affected / exposed	0 / 89 (0.00%)	0 / 95 (0.00%)	0 / 2 (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
Intestinal obstruction			
subjects affected / exposed	0 / 89 (0.00%)	0 / 95 (0.00%)	0 / 2 (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
Ascites			

subjects affected / exposed	0 / 89 (0.00%)	0 / 95 (0.00%)	1 / 2 (50.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticular perforation			
subjects affected / exposed	0 / 89 (0.00%)	0 / 95 (0.00%)	0 / 2 (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
Ileus			
subjects affected / exposed	1 / 89 (1.12%)	0 / 95 (0.00%)	0 / 2 (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
Hepatobiliary disorders			
Biliary fistula			
subjects affected / exposed	0 / 89 (0.00%)	0 / 95 (0.00%)	0 / 2 (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
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease			
subjects affected / exposed	0 / 89 (0.00%)	0 / 95 (0.00%)	0 / 2 (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
Pulmonary embolism			
subjects affected / exposed	0 / 89 (0.00%)	0 / 95 (0.00%)	0 / 2 (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			
Rheumatoid arthritis			
subjects affected / exposed	0 / 89 (0.00%)	0 / 95 (0.00%)	0 / 2 (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
Back pain			

subjects affected / exposed	0 / 89 (0.00%)	0 / 95 (0.00%)	0 / 2 (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
Infections and infestations			
Breast abscess			
subjects affected / exposed	0 / 89 (0.00%)	1 / 95 (1.05%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess limb			
subjects affected / exposed	0 / 89 (0.00%)	0 / 95 (0.00%)	0 / 2 (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
Pneumonia			
subjects affected / exposed	0 / 89 (0.00%)	0 / 95 (0.00%)	0 / 2 (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
Pyelonephritis acute			
subjects affected / exposed	0 / 89 (0.00%)	0 / 95 (0.00%)	0 / 2 (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	Phase 2 Arm C: moderate EULAR response at Week 24		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 67 (7.46%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastatic malignant melanoma			
subjects affected / exposed	0 / 67 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Invasive ductal breast carcinoma			

subjects affected / exposed	0 / 67 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract neoplasm			
subjects affected / exposed	0 / 67 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Spinal fracture			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 67 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombophlebitis			
subjects affected / exposed	0 / 67 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertensive crisis			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Pericarditis			
subjects affected / exposed	0 / 67 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute coronary syndrome			
subjects affected / exposed	0 / 67 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Coronary artery disease			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Myocardial infarction			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 67 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 67 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Duodenal perforation			
subjects affected / exposed	0 / 67 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	0 / 67 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	0 / 67 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticular perforation			

subjects affected / exposed	0 / 67 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ileus			
subjects affected / exposed	0 / 67 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Biliary fistula			
subjects affected / exposed	0 / 67 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease			
subjects affected / exposed	0 / 67 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	0 / 67 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	0 / 67 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Breast abscess			

subjects affected / exposed	0 / 67 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abscess limb			
subjects affected / exposed	0 / 67 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 67 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis acute			
subjects affected / exposed	0 / 67 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Phase 1: Tocilizumab Monotherapy	Phase 1: Combination therapy	Phase 2 Arm A2: TCZ +/- nbDMARD every two weeks (q2w)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 74 (32.43%)	119 / 327 (36.39%)	25 / 90 (27.78%)
Investigations			
Transaminases increased			
subjects affected / exposed	1 / 74 (1.35%)	37 / 327 (11.31%)	0 / 90 (0.00%)
occurrences (all)	1	42	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 74 (0.00%)	0 / 327 (0.00%)	1 / 90 (1.11%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 74 (0.00%)	0 / 327 (0.00%)	1 / 90 (1.11%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			

Neutropenia subjects affected / exposed occurrences (all)	4 / 74 (5.41%) 4	18 / 327 (5.50%) 22	5 / 90 (5.56%) 5
Thrombocytopenia subjects affected / exposed occurrences (all)	4 / 74 (5.41%) 4	9 / 327 (2.75%) 9	0 / 90 (0.00%) 0
General disorders and administration site conditions Injection site erythema subjects affected / exposed occurrences (all)	6 / 74 (8.11%) 7	10 / 327 (3.06%) 12	0 / 90 (0.00%) 0
Oedema peripheral subjects affected / exposed occurrences (all)	0 / 74 (0.00%) 0	0 / 327 (0.00%) 0	1 / 90 (1.11%) 1
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	1 / 74 (1.35%) 1	18 / 327 (5.50%) 21	0 / 90 (0.00%) 0
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	4 / 74 (5.41%) 4	15 / 327 (4.59%) 16	0 / 90 (0.00%) 0
Rheumatoid arthritis subjects affected / exposed occurrences (all)	0 / 74 (0.00%) 0	0 / 327 (0.00%) 0	3 / 90 (3.33%) 3
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 74 (2.70%) 2	23 / 327 (7.03%) 24	7 / 90 (7.78%) 9
Urinary tract infection subjects affected / exposed occurrences (all)	6 / 74 (8.11%) 8	23 / 327 (7.03%) 29	2 / 90 (2.22%) 3
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 74 (0.00%) 0	0 / 327 (0.00%) 0	4 / 90 (4.44%) 4
Respiratory tract infection			

subjects affected / exposed	0 / 74 (0.00%)	0 / 327 (0.00%)	3 / 90 (3.33%)
occurrences (all)	0	0	3

Non-serious adverse events	Phase 2 Arm A1: TCZ +/- nbDMARD once per week (qw)	Phase 2 Arm B: Participants With Low Disease Activity	Phase 2 Arm D: Non responders
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 89 (19.10%)	30 / 95 (31.58%)	0 / 2 (0.00%)
Investigations			
Transaminases increased			
subjects affected / exposed	0 / 89 (0.00%)	0 / 95 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 89 (2.25%)	5 / 95 (5.26%)	0 / 2 (0.00%)
occurrences (all)	2	5	0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 89 (2.25%)	0 / 95 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 89 (1.12%)	3 / 95 (3.16%)	0 / 2 (0.00%)
occurrences (all)	1	6	0
Thrombocytopenia			
subjects affected / exposed	0 / 89 (0.00%)	0 / 95 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	0 / 89 (0.00%)	0 / 95 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	0 / 89 (0.00%)	3 / 95 (3.16%)	0 / 2 (0.00%)
occurrences (all)	0	3	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 89 (0.00%)	0 / 95 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue			

disorders			
Back pain			
subjects affected / exposed	0 / 89 (0.00%)	0 / 95 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Rheumatoid arthritis			
subjects affected / exposed	2 / 89 (2.25%)	6 / 95 (6.32%)	0 / 2 (0.00%)
occurrences (all)	2	6	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	9 / 89 (10.11%)	3 / 95 (3.16%)	0 / 2 (0.00%)
occurrences (all)	10	4	0
Urinary tract infection			
subjects affected / exposed	3 / 89 (3.37%)	8 / 95 (8.42%)	0 / 2 (0.00%)
occurrences (all)	4	9	0
Nasopharyngitis			
subjects affected / exposed	2 / 89 (2.25%)	5 / 95 (5.26%)	0 / 2 (0.00%)
occurrences (all)	2	5	0
Respiratory tract infection			
subjects affected / exposed	2 / 89 (2.25%)	5 / 95 (5.26%)	0 / 2 (0.00%)
occurrences (all)	2	5	0

Non-serious adverse events	Phase 2 Arm C: moderate EULAR response at Week 24		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 67 (34.33%)		
Investigations			
Transaminases increased			
subjects affected / exposed	0 / 67 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	5		
Blood and lymphatic system disorders			

Neutropenia subjects affected / exposed occurrences (all)	2 / 67 (2.99%) 2		
Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 67 (0.00%) 0		
General disorders and administration site conditions Injection site erythema subjects affected / exposed occurrences (all)	0 / 67 (0.00%) 0		
Oedema peripheral subjects affected / exposed occurrences (all)	4 / 67 (5.97%) 4		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	0 / 67 (0.00%) 0		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	0 / 67 (0.00%) 0		
Rheumatoid arthritis subjects affected / exposed occurrences (all)	3 / 67 (4.48%) 3		
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	4 / 67 (5.97%) 5		
Urinary tract infection subjects affected / exposed occurrences (all)	3 / 67 (4.48%) 3		
Nasopharyngitis subjects affected / exposed occurrences (all)	4 / 67 (5.97%) 4		
Respiratory tract infection			

subjects affected / exposed	3 / 67 (4.48%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 January 2014	The purpose of the protocol amendment was to add a description of post-trial access to subcutaneous Tocilizumab (SC TCZ), to clarify that only 1 DMARD was allowed in combination with SC TCZ at the beginning of the study, to clarify that follow-up visits 4 and 8 weeks after the end of treatment was only done after study visit Week 48 and not after early withdrawal visit. The protocol was amended to explain how SC TCZ dose reduction would be done in case it was required. There was an addition of a pregnant partner release form.
22 February 2016	The purpose of the protocol amendment was to change the requirement for post-study adverse events reporting. There was also a change in the Country Study Manager.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported