



Clinical trial results:

A Randomised, open labelled study in anti-TNFα inadequate responders to investigate the mechanisms for Response - Resistance to Rituximab versus Tocilizumab in RA (R4-RA)

Summary

EudraCT number	2012-002535-28
Trial protocol	GB PT BE IT ES NL
Global end of trial date	11 July 2019

Results information

Result version number	v1 (current)
This version publication date	05 July 2020
First version publication date	05 July 2020
Summary attachment (see zip file)	SAEs occurring after treatment phase of study (SAEs after trial treatment phase.pdf)

Trial information

Trial identification

Sponsor protocol code	R4-RA
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Additional study identifiers

ISRCTN number	ISRCTN97443826
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Queen Mary University of London
Sponsor organisation address	Joint Research Management Office QM Innovation Building, 5 Walden Street, London, United Kingdom, E1 2EF
Public contact	Professor Costantino Pitzalis, Centre for Experimental Medicine and Rheumatology, Queen Mary University of London, emrclinicaltrials@qmul.ac.uk
Scientific contact	Professor Costantino Pitzalis, Centre for Experimental Medicine and Rheumatology, Queen Mary University of London, c.pitzalis@qmul.ac.uk

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	05 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 January 2019
Global end of trial reached?	Yes
Global end of trial date	11 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main aim of this project is to test the hypothesis that the presence or absence of specific synovial cellular and molecular signatures (B cells and B cell-associated signatures), assessed following a synovial tissue biopsy, will enrich for response / non-response to the B cell depleting anti-CD20 monoclonal antibody (mAb) Rituximab.

The primary aim of this project is to show that in patients failing anti-TNF therapy, with a B cell poor synovial pathotype, Rituximab is inferior to Tocilizumab therapy.

Protection of trial subjects:

Both IMPs being used in this trial are approved for use in this patient population. Infusions of Rituximab may be associated with infusion reactions of varying severity in up to 15% of patients. Most are mild and managed by slowing the rate of the Rituximab infusion. Occasionally, more severe reactions necessitate stopping the infusion and rarely, anaphylaxis has been reported. Patients will be given corticosteroids (methylprednisolone 100mg intravenous), antihistamines (chlorphenamine 10mg intravenous) and paracetamol (1000mg orally) before the infusion to minimise the risk of reactions. The risk of infection will be discussed with the patient prior to enrolment in the study however patients would be at no greater risk than routine care within the NHS.

Infusion reactions with Tocilizumab are rare. Occasionally patients may experience chills or fevers but these are self-limiting or rarely requiring paracetamol. The risk of infection will be discussed with the patient prior to enrolment in the study however patients would be at no greater risk than routine care within the NHS.

Ultrasound-guided synovial biopsy is a quick, safe and well tolerated procedure; patients who consent to the study and therefore synovial biopsy will have a longer appointment in hospital and may have discomfort from the local anaesthetic and biopsy procedure however audit data of this procedure confirms that it is well tolerated and patients are agreeable to multiple biopsies.

The risks of venepuncture may include fainting, pain and/or bruising at the site of the needle puncture. Every possible effort will be taken to minimise the potential of these risks occurring.

Background therapy:

Only entry into the trial patients should be receiving a stable dose Methotrexate for at least 4 weeks prior to biopsy visit.

Evidence for comparator:

N/A

Actual start date of recruitment	28 February 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Portugal: 9
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	United Kingdom: 109
Country: Number of subjects enrolled	Belgium: 26
Country: Number of subjects enrolled	Italy: 14
Worldwide total number of subjects	164
EEA total number of subjects	164

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)	120
From 65 to 84 years	44
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from rheumatology clinics across 19 sites in the United Kingdom, Italy, Belgium, Portugal and Spain. Recruitment began in February 2013 and ended in November 2017.

Pre-assignment

Screening details:

212 patients were approached to join the study, and 190 of these went on to consent to participation in the trial. 26 of these did not continue to randomization, 13 did not meet the inclusion criteria following the screening visit, 6 declined further participation (3 due to the biopsy), and 7 for other reasons not recorded.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Rituximab

Arm description:

Patients randomized to rituximab who received at least one dose of IMP

Arm type	Active drug
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Rituximab is available as 50ml single-use vials containing 500mg Rituximab for infusion (10mg/ml). Patients randomised to Rituximab will have an infusion cycle at baseline consisting of two infusions given 2 weeks apart (Day 0 and Day 15). A patient initially randomised to Rituximab, deemed a responder at 16 weeks (CDAI $\geq$ 50% improvement from baseline assessment) who continues to have active disease (CDAI $\geq$ 10.1) or flares (CDAI $\geq$ 10.1) will be re-treated at 24 weeks, as per the SmPC. Rituximab was prescribed according as per license and thus was sourced from local clinical supplies at each trial site.

Arm title	Tocilizumab
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Arm description:

Patients randomized to tocilizumab who received at least one dose of IMP

Arm type	Active drug
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Tocilizumab is available in 20mg/ml vials in a concentrate for intravenous infusion. Tocilizumab was prescribed according as per license and thus was sourced from local clinical supplies at each trial site. Infusions were given every 4 weeks starting at baseline with the last infusion given at 44 weeks.

Number of subjects in period 1 ^[1]	Rituximab	Tocilizumab
Started	82	79
Completed	82	79

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 212 patients were approached to join the study, and 190 of these went on to consent to participation in the trial. 26 of these did not continue to randomization, 13 did not meet the inclusion criteria following the screening visit, 6 declined further participation (3 due to the biopsy), and 7 for other reasons not recorded.

Period 2

Period 2 title	Baseline to Week 16
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Rituximab
Arm description: -	
Arm type	Active drug
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Rituximab is available as 50ml single-use vials containing 500mg Rituximab for infusion (10mg/ml). Patients randomised to Rituximab will have an infusion cycle at baseline consisting of two infusions given 2 weeks apart (Day 0 and Day 15). A patient initially randomised to Rituximab, deemed a responder at 16 weeks (CDAI $\geq$ 50% improvement from baseline assessment) who continues to have active disease (CDAI $\geq$ 10.1) or flares (CDAI $\geq$ 10.1) will be re-treated at 24 weeks, as per the SmPC. Rituximab was prescribed according as per license and thus was sourced from local clinical supplies at each trial site.

Arm title	Tocilizumab
Arm description: -	
Arm type	Active drug
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Tocilizumab is available in 20mg/ml vials in a concentrate for intravenous infusion. Tocilizumab was prescribed according as per license and thus was sourced from local clinical supplies at each trial site. Infusions were given every 4 weeks starting at baseline with the last infusion given at 44 weeks.

Number of subjects in period 2	Rituximab	Tocilizumab
Started	82	79
Completed	81	73
Not completed	1	6
Consent withdrawn by subject	-	1
Adverse event, non-fatal	1	5

Period 3

Period 3 title	Week 16 to Week 48
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Rituximab

Arm description:

Patients who were randomized to rituximab and did not switch treatment for the duration of the trial.

Arm type	Active drug
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Rituximab is available as 50ml single-use vials containing 500mg Rituximab for infusion (10mg/ml).

Patients randomised to Rituximab will have an infusion cycle at baseline consisting of two infusions given 2 weeks apart (Day 0 and Day 15). A patient initially randomised to Rituximab, deemed a responder at 16 weeks (CDAI $\geq$ 50% improvement from baseline assessment) who continues to have active disease (CDAI $\geq$ 10.1) or flares (CDAI $\geq$ 10.1) will be re-treated at 24 weeks, as per the SmPC.

Rituximab was prescribed according as per license and thus was sourced from local clinical supplies at each trial site.

Arm title	Tocilizumab
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Arm description:

Patients who were randomized to tocilizumab and did not switch treatment for the duration of the trial.

Arm type	Active drug
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Tocilizumab is available in 20mg/ml vials in a concentrate for intravenous infusion. Tocilizumab was prescribed according as per license and thus was sourced from local clinical supplies at each trial site. Infusions were given every 4 weeks starting at baseline with the last infusion given at 44 weeks.

Arm title	Rituximab+Tocilizumab
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Arm description:

Patients who were randomized to rituximab but switched to tocilizumab at week 16 or later.

Arm type	Active drug
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Rituximab is available as 50ml single-use vials containing 500mg Rituximab for infusion (10mg/ml). Patients randomised to Rituximab will have an infusion cycle at baseline consisting of two infusions given 2 weeks apart (Day 0 and Day 15). A patient initially randomised to Rituximab, deemed a responder at 16 weeks (CDAI $\geq$ 50% improvement from baseline assessment) who continues to have active disease (CDAI $\geq$ 10.1) or flares (CDAI $\geq$ 10.1) will be re-treated at 24 weeks, as per the SmPC. Rituximab was prescribed according as per license and thus was sourced from local clinical supplies at each trial site.

Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Tocilizumab is available in 20mg/ml vials in a concentrate for intravenous infusion. Tocilizumab was prescribed according as per license and thus was sourced from local clinical supplies at each trial site. Infusions were given every 4 weeks starting at baseline with the last infusion given at 44 weeks.

Arm title	Tocilizumab+Rituximab
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Arm description:

Patients who were randomized to tocilizumab and were switched to rituximab at week 16 or later

Arm type	Active drug
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Tocilizumab is available in 20mg/ml vials in a concentrate for intravenous infusion. Tocilizumab was prescribed according as per license and thus was sourced from local clinical supplies at each trial site. Infusions were given every 4 weeks starting at baseline with the last infusion given at 44 weeks.

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Rituximab is available as 50ml single-use vials containing 500mg Rituximab for infusion (10mg/ml). Patients randomised to Rituximab will have an infusion cycle at baseline consisting of two infusions given 2 weeks apart (Day 0 and Day 15). A patient initially randomised to Rituximab, deemed a responder at 16 weeks (CDAI $\geq$ 50% improvement from baseline assessment) who continues to have active disease (CDAI $\geq$ 10.1) or flares (CDAI $\geq$ 10.1) will be re-treated at 24 weeks, as per the SmPC. Rituximab was prescribed according as per license and thus was sourced from local clinical supplies at each trial site.

Number of subjects in period 3	Rituximab	Tocilizumab	Rituximab+Tocilizumab
Started	55	58	26
Completed	41	42	35
Not completed	14	16	3
Adverse event, serious fatal	1	-	-
Consent withdrawn by subject	1	2	2
Adverse event, non-fatal	-	-	-
Transferred to other arm/group	12	11	-
Pregnancy	-	1	-
Intermittent Illness	-	2	1
Lost to follow-up	-	-	-
Joined	0	0	12
Transferred in from other group/arm	-	-	12

Number of subjects in period 3	Tocilizumab+Rituximab
Started	15
Completed	18
Not completed	8
Adverse event, serious fatal	-
Consent withdrawn by subject	3
Adverse event, non-fatal	4
Transferred to other arm/group	-
Pregnancy	-
Intermittent Illness	-
Lost to follow-up	1
Joined	11
Transferred in from other group/arm	11

Baseline characteristics

Reporting groups

Reporting group title	Rituximab
Reporting group description:	
Patients randomized to rituximab who received at least one dose of IMP	
Reporting group title	Tocilizumab
Reporting group description:	
Patients randomized to tocilizumab who received at least one dose of IMP	

Reporting group values	Rituximab	Tocilizumab	Total
Number of subjects	82	79	161
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)	61	59	120
From 65-84 years	21	20	41
85 years and over	0	0	0
Age continuous			
Units: years			
median	55.72	55.50	
inter-quartile range (Q1-Q3)	47.67 to 65.54	47.36 to 65.07	-
Gender categorical			
Units: Subjects			
Female	62	66	128
Male	20	13	33
Pathotype			
Patients were assigned a histological classification based on their baseline synovial biopsy (B-cell poor, B-cell rich, Germinal centre or unknown)			
Units: Subjects			
B-cell poor	38	41	79
B-cell rich	33	31	64
Germinal centre	5	4	9
Unknown	6	3	9
Rheumatoid factor (RF) OR Anti-citrullinated protein antibody (ACPA) positive			
Units: Subjects			
Positive	70	62	132
Negative	12	17	29
Rheumatoid factor (RF) positive			
Units: Subjects			
Positive	58	47	105

Negative	24	32	56
Anti-citrullinated protein antibody (ACPA) positive Units: Subjects			
Positive	63	56	119
Negative	19	23	42
Previous Methotrexate use Units: Subjects			
Yes	82	79	161
No	0	0	0
Number of previous biologics used, [anti-TNF/Other**] Units: Subjects			
One	62	54	116
Two	14	22	36
Three or more	6	3	9
Number of concomitant DMARDs Units: Subjects			
Zero	42	43	85
One	14	17	31
Two	20	12	32
Three or more	6	7	13
Previous Prednisolone Use Units: Subjects			
Yes	44	46	90
No	38	33	71
Disease Duration Units: Years			
median	9.50	9.00	
inter-quartile range (Q1-Q3)	4.00 to 20.75	4.00 to 18.00	-
Clinical disease activity index (CDAI) Units: Score			
median	30.65	29.40	
inter-quartile range (Q1-Q3)	22.80 to 40.58	21.50 to 40.30	-
Erythrocyte sedimentation rate (ESR) Units: mm/h			
median	34.00	28.00	
inter-quartile range (Q1-Q3)	16.50 to 50.00	18.00 to 48.00	-
C-reactive protein (CRP) Units: mg/L			
median	10.00	15.10	
inter-quartile range (Q1-Q3)	5.00 to 23.00	6.00 to 32.50	-
Haemoglobin, g/L Units: g/L			
median	121.00	123.00	
inter-quartile range (Q1-Q3)	109.00 to 131.00	111.50 to 131.75	-
Number of tender joints, 0-28 Units: Score 0-28			
median	10.50	11.00	
inter-quartile range (Q1-Q3)	6.25 to 18.75	6.00 to 16.00	-
Number of swollen joints, 0-28 Units: Score 0-28			

median inter-quartile range (Q1-Q3)	6.00 4.00 to 9.00	6.00 3.00 to 10.50	-
28 joint count Disease Activity Score (DAS-28), ESR Units: Score arithmetic mean standard deviation	5.84 ± 1.19	5.78 ± 1.31	-
28 joint count Disease Activity Score (DAS-28), CRP Units: Score arithmetic mean standard deviation	5.30 ± 1.15	5.33 ± 1.26	-
Ultrasound 12-max score (Power Doppler) Units: Score median inter-quartile range (Q1-Q3)	4.00 0.25 to 8.00	6.00 1.50 to 10.00	-
Ultrasound 12-max score (Synovial Thickening) Units: Score median inter-quartile range (Q1-Q3)	16.00 13.00 to 22.00	15.00 10.00 to 20.25	-
van der Heijde modified Sharp score (SHSS), Total Units: Score median inter-quartile range (Q1-Q3)	30.00 11.00 to 70.00	24.00 9.00 to 53.00	-
van der Heijde modified Sharp score (SHSS), Joint Space Narrowing Units: score median inter-quartile range (Q1-Q3)	15.00 4.00 to 50.00	16.00 2.00 to 39.00	-
van der Heijde modified Sharp score (SHSS), Erosion Units: score median inter-quartile range (Q1-Q3)	10.00 6.00 to 23.00	10.00 3.00 to 22.00	-
Creatinine (µmol/L) Units: µmol/L median inter-quartile range (Q1-Q3)	63.00 53.00 to 73.00	59.50 54.00 to 67.75	-
Alanine aminotransferase (ALT), U/L Units: U/L median inter-quartile range (Q1-Q3)	16.00 12.00 to 21.00	16.00 12.00 to 23.00	-
Aspartate aminotransferase (AST), U/L Units: U/L median inter-quartile range (Q1-Q3)	19.00 15.00 to 22.00	18.00 16.00 to 22.00	-
Haemoglobin, g/L Units: g/L median inter-quartile range (Q1-Q3)	121.00 109.00 to 131.00	123.00 111.50 to 131.75	-
White Blood Cell count, 10 ⁹ /L			

Units: 10 ⁹ /L median inter-quartile range (Q1-Q3)	8.00 6.60 to 10.20	8.45 7.00 to 10.47	-
Platelets, 10 ⁹ /L Units: 10 ⁹ /L median inter-quartile range (Q1-Q3)	302.00 256.00 to 344.00	304.00 251.75 to 394.50	-
Neutrophils, 10 ⁹ /L Units: 10 ⁹ /L median inter-quartile range (Q1-Q3)	5.70 4.20 to 7.30	5.60 4.62 to 7.11	-
Lymphocytes, 10 ⁹ /L Units: 10 ⁹ /L median inter-quartile range (Q1-Q3)	1.70 1.20 to 2.30	1.80 1.40 to 2.40	-
Patient's global assessment—arthritis,0–100 VAS			
Patient's global assessment—arthritis,0–100 Visual Analogue Score (VAS)			
Units: score median inter-quartile range (Q1-Q3)	71.00 50.25 to 82.00	74.00 51.50 to 87.50	-
Physician's global assessment, 0–100 VAS			
Physician's global assessment, 0–100 Visual Analogue Score (VAS)			
Units: score median inter-quartile range (Q1-Q3)	60.00 49.00 to 79.75	64.00 46.00 to 76.50	-
Patient's assessment of early morning stiffness, 0–100 VAS Units: score median inter-quartile range (Q1-Q3)	35.00 20.00 to 100.00	60.00 20.00 to 100.00	-
Patient's assessment of tiredness, 0–100 VAS Units: score median inter-quartile range (Q1-Q3)	67.00 44.50 to 78.75	70.00 50.00 to 86.50	-
Patient's assessment of pain, 0–100 VAS Units: score median inter-quartile range (Q1-Q3)	66.50 48.25 to 83.50	72.00 43.00 to 87.00	-
HAQ total score			
Health assessment questionnaire (HAQ)			
Units: score median inter-quartile range (Q1-Q3)	1.75 1.25 to 2.13	1.75 1.25 to 2.13	-
Functional Assessment of Chronic Illness Therapy (FACIT) score Units: score median inter-quartile range (Q1-Q3)	23.00 15.00 to 32.00	21.00 13.00 to 33.75	-
Short form-36,Physical functioning, 0- 100			

Units: score median inter-quartile range (Q1-Q3)	30.00 10.00 to 48.75	30.00 15.00 to 45.00	-
Short form-36, Physical role functioning, 0-100 Units: score median inter-quartile range (Q1-Q3)	0.00 0.00 to 25.00	0.00 0.00 to 0.00	-
Short form-36, Emotional role functioning, 0-100 Units: score median inter-quartile range (Q1-Q3)	33.33 0.00 to 91.67	0.00 0.00 to 66.67	-
Short form-36, Vitality, 0-100 Units: score median inter-quartile range (Q1-Q3)	35.00 20.00 to 50.00	30.00 20.00 to 45.00	-
Short form-36, Mental health, 0-100 Units: score arithmetic mean standard deviation	61.22 ± 19.08	58.73 ± 20.66	-
Short form-36, Social role functioning, 0-100 Units: score median inter-quartile range (Q1-Q3)	37.50 25.00 to 62.50	50.00 25.00 to 75.00	-
Short form-36, Bodily pain, 0-100 Units: score median inter-quartile range (Q1-Q3)	22.50 22.50 to 45.00	22.50 10.00 to 45.00	-
Short form-36, General health perceptions, 0-100 Units: score median inter-quartile range (Q1-Q3)	35.00 25.00 to 45.00	35.00 25.00 to 50.00	-

End points

End points reporting groups

Reporting group title	Rituximab
Reporting group description: Patients randomized to rituximab who received at least one dose of IMP	
Reporting group title	Tocilizumab
Reporting group description: Patients randomized to tocilizumab who received at least one dose of IMP	
Reporting group title	Rituximab
Reporting group description: -	
Reporting group title	Tocilizumab
Reporting group description: -	
Reporting group title	Rituximab
Reporting group description: Patients who were randomized to rituximab and did not switch treatment for the duration of the trial.	
Reporting group title	Tocilizumab
Reporting group description: Patients who were randomized to tocilizumab and did not switch treatment for the duration of the trial.	
Reporting group title	Rituximab+Tocilizumab
Reporting group description: Patients who were randomized to rituximab but switched to tocilizumab at week 16 or later.	
Reporting group title	Tocilizumab+Rituximab
Reporting group description: Patients who were randomized to tocilizumab and were switched to rituximab at week 16 or later	
Subject analysis set title	SAF
Subject analysis set type	Safety analysis
Subject analysis set description: Safety analysis set	
Subject analysis set title	ITT week 16 - B cell poor Rituximab
Subject analysis set type	Intention-to-treat
Subject analysis set description: Subgroup of patients classified as B cell poor by histology classification and analysed as ITT at week 16	
Subject analysis set title	ITT week 16 - B cell poor Tocilizumab
Subject analysis set type	Intention-to-treat
Subject analysis set description: Subgroup of patients classified as B cell poor by histology classification and analysed as ITT at week 16	
Subject analysis set title	ITT week 16 - B cell rich Rituximab
Subject analysis set type	Intention-to-treat
Subject analysis set description: Subgroup of patients classified as B cell rich by histology classification and analysed as ITT at week 16	
Subject analysis set title	ITT week 16 - B cell rich Tocilizumab
Subject analysis set type	Intention-to-treat
Subject analysis set description: Subgroup of patients classified as B cell rich by histology classification and analysed as ITT at week 16	
Subject analysis set title	ITT week 16 - B cell poor (RNA_seq) Rituximab
Subject analysis set type	Intention-to-treat
Subject analysis set description: Subgroup of patients classified as B cell poor by RNA-seq classification and analysed as ITT at week 16	

Subject analysis set title	ITT week 16 - B cell poor (RNA_seq) Tocilizumab
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subgroup of patients classified as B cell poor by RNA-sequencing classification and analysed as ITT at week 16	
Subject analysis set title	ITT week 16 - B cell rich (RNA_seq) Rituximab
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subgroup of patients classified as B cell rich by RNA-sequencing classification and analysed as ITT at week 16	
Subject analysis set title	ITT week 16 - B cell rich (RNA_seq) Tocilizumab
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subgroup of patients classified as B cell rich by RNA-sequencing classification and analysed as ITT at week 16	
Subject analysis set title	PP week 16 - B cell poor Rituximab
Subject analysis set type	Per protocol
Subject analysis set description:	
Subgroup of patients classified as B cell poor by histology classification and analysed as PP at week 16	
Subject analysis set title	PP week 16 - B cell poor Tocilizumab
Subject analysis set type	Per protocol
Subject analysis set description:	
Subgroup of patients classified as B cell poor by histology classification and analysed as PP at week 16	
Subject analysis set title	PP week 16 - B cell rich Rituximab
Subject analysis set type	Per protocol
Subject analysis set description:	
Subgroup of patients classified as B cell rich by histology classification and analysed as PP at week 16	
Subject analysis set title	PP week 16 - B cell rich Tocilizumab
Subject analysis set type	Per protocol
Subject analysis set description:	
Subgroup of patients classified as B cell rich by histology classification and analysed as PP at week 16	
Subject analysis set title	PP week 16 - B cell poor (RNA_seq) Rituximab
Subject analysis set type	Per protocol
Subject analysis set description:	
Subgroup of patients classified as B cell poor by RNA sequencing classification and analysed as PP at week 16	
Subject analysis set title	PP week 16 - B cell poor (RNA_seq) Tocilizumab
Subject analysis set type	Per protocol
Subject analysis set description:	
Subgroup of patients classified as B cell poor by RNA-sequencing classification and analysed as PP at week 16	
Subject analysis set title	PP week 16 - B cell rich (RNA_seq) Rituximab
Subject analysis set type	Per protocol
Subject analysis set description:	
Subgroup of patients classified as B cell rich by RNA-sequencing classification and analysed as PP at week 16	
Subject analysis set title	PP week 16 - B cell rich (RNA_seq) Tocilizumab
Subject analysis set type	Per protocol
Subject analysis set description:	
Subgroup of patients classified as B cell rich by RNA-sequencing classification and analysed as PP at week 16	
Subject analysis set title	week 24 - B cell poor Rituximab
Subject analysis set type	Per protocol

Subject analysis set description:

Subgroup of patients classified as B cell poor by histology classification and analysed as PP at week 24

Subject analysis set title	week 24 - B cell poor Tocilizumab
Subject analysis set type	Per protocol

Subject analysis set description:

Subgroup of patients classified as B cell poor by histology classification and analysed as PP at week 24

Subject analysis set title	week 24 - B cell rich Rituximab
Subject analysis set type	Per protocol

Subject analysis set description:

Subgroup of patients classified as B cell rich by histology classification and analysed as PP at week 24

Subject analysis set title	week 24 - B cell rich Tocilizumab
Subject analysis set type	Per protocol

Subject analysis set description:

Subgroup of patients classified as B cell rich by histology classification and analysed as PP at week 24

Subject analysis set title	week 36 - B cell poor Rituximab
Subject analysis set type	Per protocol

Subject analysis set description:

Subgroup of patients classified as B cell poor by histology classification and analysed as PP at week 36

Subject analysis set title	week 36 - B cell poor Tocilizumab
Subject analysis set type	Per protocol

Subject analysis set description:

Subgroup of patients classified as B cell poor by histology classification and analysed as PP at week 36

Subject analysis set title	week 36 - B cell rich Rituximab
Subject analysis set type	Per protocol

Subject analysis set description:

Subgroup of patients classified as B cell rich by histology classification and analysed as PP at week 36

Subject analysis set title	week 36 - B cell rich Tocilizumab
Subject analysis set type	Per protocol

Subject analysis set description:

Subgroup of patients classified as B cell rich by histology classification and analysed as PP at week 36

Subject analysis set title	week 48 - B cell poor Rituximab
Subject analysis set type	Per protocol

Subject analysis set description:

Subgroup of patients classified as B cell poor by histology classification and analysed as PP at week 48

Subject analysis set title	week 48 - B cell poor Tocilizumab
Subject analysis set type	Per protocol

Subject analysis set description:

Subgroup of patients classified as B cell poor by histology classification and analysed as PP at week 48

Subject analysis set title	week 48 - B cell rich Rituximab
Subject analysis set type	Per protocol

Subject analysis set description:

Subgroup of patients classified as B cell rich by histology classification and analysed as PP at week 48

Subject analysis set title	week 48 - B cell rich Tocilizumab
Subject analysis set type	Per protocol

Subject analysis set description:

Subgroup of patients classified as B cell rich by histology classification and analysed as PP at week 48

Subject analysis set title	RTX+TOC, B cell poor, 16 weeks after
Subject analysis set type	Per protocol

Subject analysis set description:

B cell poor patients who were non responders at visit 7-8 were switched to the other IMP and response was evaluated 16 weeks after this switch

Subject analysis set title	RTX+TOC, B cell rich, 16 weeks after
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Subject analysis set type	Per protocol
Subject analysis set description: B cell rich patients who were non responders at visit 7-8 were switched to the other IMP and response was evaluated 16 weeks after this switch	
Subject analysis set title	TOC+RTX, B cell poor, 16 weeks after
Subject analysis set type	Per protocol
Subject analysis set description: B cell poor patients who were non responders at visit 7-8 were switched to the other IMP and response was evaluated 16 weeks after this switch	
Subject analysis set title	TOC+RTX, B cell rich, 16 weeks after
Subject analysis set type	Per protocol
Subject analysis set description: B cell rich patients who were non responders at visit 7-8 were switched to the other IMP and response was evaluated 16 weeks after this switch	

Primary: CDAI 50% Improvement

End point title	CDAI 50% Improvement
End point description: Patients are deemed as Responders if their CDAI decreased by 50% or more from baseline	
End point type	Primary
End point timeframe: Period 2: Baseline to Week 16 Period 3: Week 16 to Week 48	

End point values	Rituximab	Tocilizumab	Rituximab	Tocilizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82	79	42	42
Units: Responders				
Responder	37	44	30	33

End point values	ITT week 16 - B cell poor Rituximab	ITT week 16 - B cell poor Tocilizumab	ITT week 16 - B cell rich Rituximab	ITT week 16 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	38	41	33	31
Units: Responders				
Responder	17	23	13	16

End point values	ITT week 16 - B cell poor (RNA_seq) Rituximab	ITT week 16 - B cell poor (RNA_seq) Tocilizumab	ITT week 16 - B cell rich (RNA_seq) Rituximab	ITT week 16 - B cell rich (RNA_seq) Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	32	30	29
Units: Responders				

Responder	12	20	15	14
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End point values	PP week 16 - B cell poor Rituximab	PP week 16 - B cell poor Tocilizumab	PP week 16 - B cell rich Rituximab	PP week 16 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	30	31	23
Units: Responders				
Responder	16	21	12	12

End point values	PP week 16 - B cell poor (RNA_seq) Rituximab	PP week 16 - B cell poor (RNA_seq) Tocilizumab	PP week 16 - B cell rich (RNA_seq) Rituximab	PP week 16 - B cell rich (RNA_seq) Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	32	25	28	19
Units: Responders				
Responder	11	19	14	9

End point values	week 24 - B cell poor Rituximab	week 24 - B cell poor Tocilizumab	week 24 - B cell rich Rituximab	week 24 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	21	27	18	20
Units: Responders				
Responder	11	21	10	14

End point values	week 36 - B cell poor Rituximab	week 36 - B cell poor Tocilizumab	week 36 - B cell rich Rituximab	week 36 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	22	17	16
Units: Responders				
Responder	14	16	10	14

End point values	week 48 - B cell poor Rituximab	week 48 - B cell poor Tocilizumab	week 48 - B cell rich Rituximab	week 48 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17	21	17	16
Units: Responders				
Responder	15	16	9	13

End point values	RTX+TOC, B cell poor, 16 weeks after	RTX+TOC, B cell rich, 16 weeks after	TOC+RTX, B cell poor, 16 weeks after	TOC+RTX, B cell rich, 16 weeks after
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	14	13	8	7
Units: Responders				
Responder	4	5	2	3

Statistical analyses

Statistical analysis title	Primary: TOC vs. RTX, B cell poor, ITT
Comparison groups	ITT week 16 - B cell poor Rituximab v ITT week 16 - B cell poor Tocilizumab
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.31
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.114
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.106
upper limit	0.333

Statistical analysis title	TOC vs. RTX, B cell rich, ITT
Comparison groups	ITT week 16 - B cell rich Rituximab v ITT week 16 - B cell rich Tocilizumab
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.33
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.122
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.365

Statistical analysis title	TOC vs. RTX, B cell poor (RNA-seq), ITT
Comparison groups	ITT week 16 - B cell poor (RNA_seq) Rituximab v ITT week 16 - B cell poor (RNA_seq) Tocilizumab
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.035
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.261
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.027
upper limit	0.496

Statistical analysis title	TOC vs. RTX, B cell rich (RNA-seq), ITT
Comparison groups	ITT week 16 - B cell rich (RNA_seq) Rituximab v ITT week 16 - B cell rich (RNA_seq) Tocilizumab
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.89
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	-0.017
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.272
upper limit	0.238

Statistical analysis title	TOC vs. RTX, B cell poor, PP
Comparison groups	PP week 16 - B cell poor Rituximab v PP week 16 - B cell poor Tocilizumab
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.029
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.268
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.039
upper limit	0.496

Statistical analysis title	TOC vs. RTX, B cell rich, PP
Comparison groups	PP week 16 - B cell rich Rituximab v PP week 16 - B cell rich Tocilizumab
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.32
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.135
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.132
upper limit	0.401

Statistical analysis title	TOC vs. RTX, B cell poor (RNA-seq), PP
Comparison groups	PP week 16 - B cell poor (RNA_seq) Rituximab v PP week 16 - B cell poor (RNA_seq) Tocilizumab
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0018
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.416
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.181
upper limit	0.651

Statistical analysis title	TOC vs. RTX, B cell rich (RNA-seq), PP
Comparison groups	PP week 16 - B cell rich (RNA_seq) RiItuximab v PP week 16 - B cell rich (RNA_seq) Tocilizumab
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.86
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	-0.026

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.317
upper limit	0.265

Statistical analysis title	RTX+TOC vs. TOC+RTX, B cell poor, week 16/20 +16
Statistical analysis description:	
Comparison of response in patients who switched treatment	
Comparison groups	RTX+TOC, B cell poor, 16 weeks after v TOC+RTX, B cell poor, 16 weeks after
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact

Statistical analysis title	RTX+TOC vs. TOC+RTX, B cell rich, week 16/20 + 16
Statistical analysis description:	
Comparison of response in patients who switched treatment	
Comparison groups	RTX+TOC, B cell rich, 16 weeks after v TOC+RTX, B cell rich, 16 weeks after
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact

Statistical analysis title	TOC vs. RTX, B cell poor, week 24
Comparison groups	week 24 - B cell poor Rituximab v week 24 - B cell poor Tocilizumab
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.284
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.022
upper limit	0.546

Statistical analysis title	TOC vs. RTX, B cell rich, week 24
Comparison groups	week 24 - B cell rich Rituximab v week 24 - B cell rich Tocilizumab
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.181
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.122
upper limit	0.484

Statistical analysis title	TOC vs. RTX, B cell poor, week 36
Comparison groups	week 36 - B cell poor Rituximab v week 36 - B cell poor Tocilizumab
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.027
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.247
upper limit	0.301

Statistical analysis title	TOC vs. RTX, B cell rich, week 36
Comparison groups	week 36 - B cell rich Rituximab v week 36 - B cell rich Tocilizumab
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.267

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.003
upper limit	0.537

Statistical analysis title	TOC vs. RTX, B cell poor, week 48
Comparison groups	week 48 - B cell poor Rituximab v week 48 - B cell poor Tocilizumab
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	-0.082
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.315
upper limit	0.15

Statistical analysis title	TOC vs. RTX, B cell rich, week 48
Comparison groups	week 48 - B cell rich Rituximab v week 48 - B cell rich Tocilizumab
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.283
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.022
upper limit	0.588

Statistical analysis title	TOC vs. RTX, week 16
Statistical analysis description:	
Any pathotype	
Comparison groups	Rituximab v Tocilizumab

Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.106
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.048
upper limit	0.259

Statistical analysis title	TOC vs. RTX, week 48
Statistical analysis description:	
Any pathotype	
Comparison groups	Rituximab v Tocilizumab
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.091
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.092
upper limit	0.273

Primary: Ultrasound Power Doppler 12-max score, change from baseline	
End point title	Ultrasound Power Doppler 12-max score, change from baseline
End point description:	
End point type	Primary
End point timeframe:	
Timeframe 2: Week 16	
Timeframe 3: Week 48	

End point values	Rituximab	Tocilizumab	Rituximab	Tocilizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82	79	42	42
Units: values				
least squares mean (standard error)	-0.5 (± 0.7)	-2.1 (± 0.8)	-4.99 (± 0.74)	-5.72 (± 0.74)

End point values	ITT week 16 - B cell poor Rituximab	ITT week 16 - B cell poor Tocilizumab	ITT week 16 - B cell rich Rituximab	ITT week 16 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	38	41	33	31
Units: values				
least squares mean (standard error)	0.3 (± 1.1)	-1.1 (± 1.1)	-1.4 (± 1.0)	-2.8 (± 1.1)

End point values	ITT week 16 - B cell poor (RNA_seq) Rituximab	ITT week 16 - B cell poor (RNA_seq) Tocilizumab	ITT week 16 - B cell rich (RNA_seq) Rituximab	ITT week 16 - B cell rich (RNA_seq) Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	32	30	29
Units: values				
least squares mean (standard error)	0.1 (± 1.1)	-1.2 (± 1.1)	-0.6 (± 1.3)	-2.9 (± 1.4)

End point values	PP week 16 - B cell poor Rituximab	PP week 16 - B cell poor Tocilizumab	PP week 16 - B cell rich Rituximab	PP week 16 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	30	31	23
Units: values				
least squares mean (standard error)	0.1 (± 1.1)	-2.4 (± 1.4)	-1.5 (± 1.1)	-2.9 (± 1.3)

End point values	PP week 16 - B cell poor (RNA_seq) Rituximab	PP week 16 - B cell poor (RNA_seq) Tocilizumab	PP week 16 - B cell rich (RNA_seq) Rituximab	PP week 16 - B cell rich (RNA_seq) Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	32	25	28	19
Units: values				
least squares mean (standard error)	-0.2 (± 1.2)	-1.9 (± 1.3)	-0.6 (± 1.4)	-3.0 (± 1.7)

End point values	week 48 - B cell poor	week 48 - B cell poor	week 48 - B cell rich	week 48 - B cell rich
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	Rituximab	Tocilizumab	Rituximab	Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17	21	17	16
Units: values				
least squares mean (standard error)	-4.9 ($\pm$ 1.54)	-6.46 ($\pm$ 1.79)	-5.42 ($\pm$ 0.98)	-5.8 ($\pm$ 0.98)

Statistical analyses

Statistical analysis title	TOC vs. RTX, B cell poor, ITT
Comparison groups	ITT week 16 - B cell poor Rituximab v ITT week 16 - B cell poor Tocilizumab
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	4.8

Statistical analysis title	TOC vs. RTX, B cell rich, ITT
Comparison groups	ITT week 16 - B cell rich Rituximab v ITT week 16 - B cell rich Tocilizumab
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.38
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	4.6

Statistical analysis title	TOC vs. RTX, B cell poor (RNA seq), ITT
Comparison groups	ITT week 16 - B cell poor (RNA_seq) Rituximab v ITT week 16 - B cell poor (RNA_seq) Tocilizumab

Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.41
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	4.7

Statistical analysis title	TOC vs. RTX, B cell rich (RNA seq), ITT
Comparison groups	ITT week 16 - B cell rich (RNA_seq) Rituximab v ITT week 16 - B cell rich (RNA_seq) Tocilizumab
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.25
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	6.4

Statistical analysis title	TOC vs. RTX, B cell poor, PP
Comparison groups	PP week 16 - B cell poor Rituximab v PP week 16 - B cell poor Tocilizumab
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.19
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	6.5

Statistical analysis title	TOC vs. RTX, B cell rich, PP
Comparison groups	PP week 16 - B cell rich Rituximab v PP week 16 - B cell rich Tocilizumab
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	4.9

Statistical analysis title	TOC vs. RTX, B cell poor (RNA seq), PP
Comparison groups	PP week 16 - B cell poor (RNA_seq) Rituximab v PP week 16 - B cell poor (RNA_seq) Tocilizumab
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.34
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	5.6

Statistical analysis title	TOC vs. RTX, B cell rich (RNA seq), PP
Comparison groups	PP week 16 - B cell rich (RNA_seq) Rituximab v PP week 16 - B cell rich (RNA_seq) Tocilizumab
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.29
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	7.1

Secondary: Target CDAI (<10.1)

End point title	Target CDAI (<10.1)
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End point description:

End point type	Secondary
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End point timeframe:

Period 2: Baseline to Week 16

Period 3: Week 16 to Week 48

End point values	Rituximab	Tocilizumab	Rituximab	Tocilizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82	79	42	42
Units: Patients				
Responder	21	36	21	31

End point values	ITT week 16 - B cell poor Rituximab	ITT week 16 - B cell poor Tocilizumab	ITT week 16 - B cell rich Rituximab	ITT week 16 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	38	41	33	31
Units: Patients				
Responder	11	19	7	12

End point values	ITT week 16 - B cell poor (RNA_seq) Rituximab	ITT week 16 - B cell poor (RNA_seq) Tocilizumab	ITT week 16 - B cell rich (RNA_seq) Rituximab	ITT week 16 - B cell rich (RNA_seq) Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	32	30	29
Units: Patients				
Responder	5	16	10	10

End point values	PP week 16 - B cell poor Rituximab	PP week 16 - B cell poor Tocilizumab	PP week 16 - B cell rich Rituximab	PP week 16 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	30	31	23
Units: Patients				
Responder	11	17	7	8

End point values	PP week 16 - B cell poor (RNA_seq) Rituximab	PP week 16 - B cell poor (RNA_seq) Tocilizumab	PP week 16 - B cell rich (RNA_seq) Rituximab	PP week 16 - B cell rich (RNA_seq) Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	32	25	28	19
Units: Patients				
Responder	5	15	10	5

End point values	week 24 - B cell poor Rituximab	week 24 - B cell poor Tocilizumab	week 24 - B cell rich Rituximab	week 24 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	21	27	18	20
Units: Patients				
Responder	6	16	5	10

End point values	week 36 - B cell poor Rituximab	week 36 - B cell poor Tocilizumab	week 36 - B cell rich Rituximab	week 36 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	22	17	16
Units: Patients				
Responder	9	13	8	11

End point values	week 48 - B cell poor Rituximab	week 48 - B cell poor Tocilizumab	week 48 - B cell rich Rituximab	week 48 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17	21	17	16
Units: Patients				
Responder	11	14	7	12

Statistical analyses

Statistical analysis title	TOC vs. RTX, B cell poor, ITT
Comparison groups	ITT week 16 - B cell poor Rituximab v ITT week 16 - B cell poor Tocilizumab

Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.11
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.174
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.036
upper limit	0.384

Statistical analysis title	TOC vs. RTX, B cell rich, ITT
Comparison groups	ITT week 16 - B cell rich Rituximab v ITT week 16 - B cell rich Tocilizumab
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.13
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.175
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.046
upper limit	0.396

Statistical analysis title	TOC vs. RTX, B cell poor (RNA seq), ITT
Comparison groups	ITT week 16 - B cell poor (RNA_seq) Rituximab v ITT week 16 - B cell poor (RNA_seq) Tocilizumab
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0036
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.348
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.136
upper limit	0.561

Statistical analysis title	TOC vs. RTX, B cell rich (RNA seq), ITT
Comparison groups	ITT week 16 - B cell rich (RNA_seq) Rituximab v ITT week 16 - B cell rich (RNA_seq) Tocilizumab
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.93
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.011
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	0.253

Statistical analysis title	TOC vs. RTX, B cell poor, PP
Comparison groups	PP week 16 - B cell poor Rituximab v PP week 16 - B cell poor Tocilizumab
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.026
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.269
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.039
upper limit	0.5

Statistical analysis title	TOC vs. RTX, B cell rich, PP
Comparison groups	PP week 16 - B cell rich Rituximab v PP week 16 - B cell rich Tocilizumab
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.32
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.122
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.122
upper limit	0.366

Statistical analysis title	TOC vs. RTX, B cell poor (RNA seq), PP
Comparison groups	PP week 16 - B cell poor (RNA_seq) Rituximab v PP week 16 - B cell poor (RNA_seq) Tocilizumab
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00073
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.444
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.214
upper limit	0.673

Statistical analysis title	TOC vs. RTX, B cell rich (RNA seq), PP
Comparison groups	PP week 16 - B cell rich (RNA_seq) Rituximab v PP week 16 - B cell rich (RNA_seq) Tocilizumab
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.54
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	-0.094
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.36
upper limit	0.172

Secondary: DAS28 (ESR) ≤ 3.2

End point title	DAS28 (ESR) ≤ 3.2
End point description:	
End point type	Secondary
End point timeframe:	
Timeframe 2: Week 16	
Timeframe 3: Week 48	

End point values	Rituximab	Tocilizumab	Rituximab	Tocilizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82	79	42	42
Units: Responders				
Responders	21	36	20	33

End point values	ITT week 16 - B cell poor Rituximab	ITT week 16 - B cell poor Tocilizumab	ITT week 16 - B cell rich Rituximab	ITT week 16 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	38	41	33	31
Units: Responders				
Responders	10	18	8	13

End point values	ITT week 16 - B cell poor (RNA_seq) Rituximab	ITT week 16 - B cell poor (RNA_seq) Tocilizumab	ITT week 16 - B cell rich (RNA_seq) Rituximab	ITT week 16 - B cell rich (RNA_seq) Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	32	30	29
Units: Responders				
Responders	6	17	9	10

End point values	PP week 16 - B cell poor Rituximab	PP week 16 - B cell poor Tocilizumab	PP week 16 - B cell rich Rituximab	PP week 16 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	30	31	23
Units: Responders				
Responders	10	14	8	11

End point values	PP week 16 - B cell poor (RNA_seq) Rituximab	PP week 16 - B cell poor (RNA_seq) Tocilizumab	PP week 16 - B cell rich (RNA_seq) Rituximab	PP week 16 - B cell rich (RNA_seq) Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	32	25	28	19
Units: Responders				
Responders	6	15	9	7

End point values	week 24 - B cell poor	week 24 - B cell poor	week 24 - B cell rich	week 24 - B cell rich
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	Rituximab	Tocilizumab	Rituximab	Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	21	27	18	20
Units: Responders				
Responders	7	17	6	13

End point values	week 36 - B cell poor Rituximab	week 36 - B cell poor Tocilizumab	week 36 - B cell rich Rituximab	week 36 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	22	17	16
Units: Responders				
Responders	8	14	9	11

End point values	week 48 - B cell poor Rituximab	week 48 - B cell poor Tocilizumab	week 48 - B cell rich Rituximab	week 48 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17	21	17	16
Units: Responders				
Responders	8	16	9	12

Statistical analyses

Statistical analysis title	TOC vs. RTX, B cell poor, ITT
Comparison groups	ITT week 16 - B cell poor Rituximab v ITT week 16 - B cell poor Tocilizumab
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.176
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.031
upper limit	0.382

Statistical analysis title	TOC vs. RTX, B cell rich, ITT
Comparison groups	ITT week 16 - B cell rich Rituximab v ITT week 16 - B cell rich Tocilizumab

Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.13
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.177
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.404

Statistical analysis title	TOC vs. RTX, B cell poor (RNA seq), ITT
Comparison groups	ITT week 16 - B cell poor (RNA_seq) Rituximab v ITT week 16 - B cell poor (RNA_seq) Tocilizumab
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0032
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.349
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.132
upper limit	0.567

Statistical analysis title	TOC vs. RTX, B cell rich (RNA seq), ITT
Comparison groups	ITT week 16 - B cell rich (RNA_seq) Tocilizumab v ITT week 16 - B cell rich (RNA_seq) Rituximab
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.71
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.045
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.194
upper limit	0.283

Statistical analysis title	TOC vs. RTX, B cell poor, PP
Comparison groups	PP week 16 - B cell poor Rituximab v PP week 16 - B cell poor Tocilizumab
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.095
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.196
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.032
upper limit	0.425

Statistical analysis title	TOC vs. RTX, B cell rich, PP
Comparison groups	PP week 16 - B cell rich Rituximab v PP week 16 - B cell rich Tocilizumab
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.094
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.036
upper limit	0.476

Statistical analysis title	TOC vs. RTX, B cell poor (RNA seq), PP
Comparison groups	PP week 16 - B cell poor (RNA_seq) Rituximab v PP week 16 - B cell poor (RNA_seq) Tocilizumab
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0014
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.412
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.178
upper limit	0.647

Statistical analysis title	TOC vs. RTX, B cell rich (RNA seq), PP
Comparison groups	PP week 16 - B cell rich (RNA_seq) RItuximab v PP week 16 - B cell rich (RNA_seq) Tocilizumab
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.74
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.047
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	0.324

Secondary: DAS28 (CRP) <= 3.2

End point title	DAS28 (CRP) <= 3.2
End point description:	
End point type	Secondary
End point timeframe:	
Timeframe 2: Week 16	
Timeframe 3: Week 48	

End point values	Rituximab	Tocilizumab	Rituximab	Tocilizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82	79	42	42
Units: Responders				
Responders	26	37	18	30

End point values	ITT week 16 - B cell poor Rituximab	ITT week 16 - B cell poor Tocilizumab	ITT week 16 - B cell rich Rituximab	ITT week 16 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	38	41	33	31
Units: Responders				
Responders	12	19	12	13

End point values	ITT week 16 - B cell poor (RNA_seq) Rituximab	ITT week 16 - B cell poor (RNA_seq) Tocilizumab	ITT week 16 - B cell rich (RNA_seq) Rituximab	ITT week 16 - B cell rich (RNA_seq) Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	32	30	29
Units: Responders				
Responders	7	16	14	11

End point values	PP week 16 - B cell poor Rituximab	PP week 16 - B cell poor Tocilizumab	PP week 16 - B cell rich Rituximab	PP week 16 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	30	31	23
Units: Responders				
Responders	12	16	10	10

End point values	PP week 16 - B cell poor (RNA_seq) Rituximab	PP week 16 - B cell poor (RNA_seq) Tocilizumab	PP week 16 - B cell rich (RNA_seq) Rituximab	PP week 16 - B cell rich (RNA_seq) Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	32	25	28	19
Units: Responders				
Responders	7	15	12	7

End point values	week 24 - B cell poor Rituximab	week 24 - B cell poor Tocilizumab	week 24 - B cell rich Rituximab	week 24 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	21	27	18	20
Units: Responders				
Responders	9	17	10	13

End point values	week 36 - B cell poor Rituximab	week 36 - B cell poor Tocilizumab	week 36 - B cell rich Rituximab	week 36 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	22	17	16
Units: Responders				
Responders	11	14	7	12

End point values	week 48 - B cell poor Rituximab	week 48 - B cell poor Tocilizumab	week 48 - B cell rich Rituximab	week 48 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17	21	17	16
Units: Responders				
Responders	9	13	7	12

Statistical analyses

Statistical analysis title	TOC vs. RTX, B cell poor, ITT
Comparison groups	ITT week 16 - B cell poor Rituximab v ITT week 16 - B cell poor Tocilizumab
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.18
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.148
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.065
upper limit	0.36

Statistical analysis title	TOC vs. RTX, B cell rich, ITT
Comparison groups	ITT week 16 - B cell rich Rituximab v ITT week 16 - B cell rich Tocilizumab
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.65
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.056
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.183
upper limit	0.295

Statistical analysis title	TOC vs. RTX, B cell poor (RNA seq), ITT
Comparison groups	ITT week 16 - B cell poor (RNA_seq) Rituximab v ITT week 16 - B cell poor (RNA_seq) Tocilizumab
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.288
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.065
upper limit	0.51

Statistical analysis title	TOC vs. RTX, B cell rich (RNA seq), ITT
Comparison groups	ITT week 16 - B cell rich (RNA_seq) Rituximab v ITT week 16 - B cell rich (RNA_seq) Tocilizumab
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	-0.087
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.338
upper limit	0.164

Statistical analysis title	TOC vs. RTX, B cell poor, PP
Comparison groups	PP week 16 - B cell poor Rituximab v PP week 16 - B cell poor Tocilizumab
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.085
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.209
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.025
upper limit	0.443

Statistical analysis title	TOC vs. RTX, B cell rich, PP
Comparison groups	PP week 16 - B cell rich Rituximab v PP week 16 - B cell rich Tocilizumab
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.112
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.149
upper limit	0.373

Statistical analysis title	TOC vs. RTX, B cell poor (RNA seq), PP
Comparison groups	PP week 16 - B cell poor (RNA_seq) Rituximab v PP week 16 - B cell poor (RNA_seq) Tocilizumab
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0033
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.381
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.142
upper limit	0.621

Statistical analysis title	TOC vs. RTX, B cell rich (RNA seq), PP
Comparison groups	PP week 16 - B cell rich (RNA_seq) Rituximab v PP week 16 - B cell rich (RNA_seq) Tocilizumab
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.68
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	-0.06

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.344
upper limit	0.224

Secondary: DAS28 (ESR) <= 2.6

End point title DAS28 (ESR) <= 2.6

End point description:

End point type Secondary

End point timeframe:

Timeframe 2: Week 16

Timeframe 3: Week 48

End point values	Rituximab	Tocilizumab	Rituximab	Tocilizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82	79	42	42
Units: Responders				
Responders	10	31	9	30

End point values	ITT week 16 - B cell poor Rituximab	ITT week 16 - B cell poor Tocilizumab	ITT week 16 - B cell rich Rituximab	ITT week 16 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	38	41	33	31
Units: Responders				
Responders	6	15	2	11

End point values	ITT week 16 - B cell poor (RNA_seq) Rituximab	ITT week 16 - B cell poor (RNA_seq) Tocilizumab	ITT week 16 - B cell rich (RNA_seq) Rituximab	ITT week 16 - B cell rich (RNA_seq) Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	32	30	29
Units: Responders				
Responders	3	13	3	10

End point values	PP week 16 - B cell poor	PP week 16 - B cell poor	PP week 16 - B cell rich	PP week 16 - B cell rich
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	Rituximab	Tocilizumab	Rituximab	Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	30	31	23
Units: Responders				
Responders	6	13	2	9

End point values	PP week 16 - B cell poor (RNA_seq) Rituximab	PP week 16 - B cell poor (RNA_seq) Tocilizumab	PP week 16 - B cell rich (RNA_seq) Rituximab	PP week 16 - B cell rich (RNA_seq) Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	32	25	28	19
Units: Responders				
Responders	3	12	3	7

End point values	week 24 - B cell poor Rituximab	week 24 - B cell poor Tocilizumab	week 24 - B cell rich Rituximab	week 24 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	21	27	18	20
Units: Responders				
Responders	3	14	2	9

End point values	week 36 - B cell poor Rituximab	week 36 - B cell poor Tocilizumab	week 36 - B cell rich Rituximab	week 36 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	22	17	16
Units: Responders				
Responders	5	10	3	10

End point values	week 48 - B cell poor Rituximab	week 48 - B cell poor Tocilizumab	week 48 - B cell rich Rituximab	week 48 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17	21	17	16
Units: Responders				
Responders	3	13	4	12

Statistical analyses

Statistical analysis title	TOC vs. RTX, B cell poor, ITT
Comparison groups	ITT week 16 - B cell poor Tocilizumab v ITT week 16 - B cell poor Rituximab
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.037
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.208
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.396

Statistical analysis title	TOC vs. RTX, B cell rich, ITT
Comparison groups	ITT week 16 - B cell rich Rituximab v ITT week 16 - B cell rich Tocilizumab
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0047
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.294
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.107
upper limit	0.481

Statistical analysis title	TOC vs. RTX, B cell poor (RNA seq), ITT
Comparison groups	ITT week 16 - B cell poor (RNA_seq) Rituximab v ITT week 16 - B cell poor (RNA_seq) Tocilizumab
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.315
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.119
upper limit	0.512

Statistical analysis title	TOC vs. RTX, B cell rich (RNA seq), ITT
Comparison groups	ITT week 16 - B cell rich (RNA_seq) Rituximab v ITT week 16 - B cell rich (RNA_seq) Tocilizumab
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.245
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.041
upper limit	0.448

Statistical analysis title	TOC vs. RTX, B cell poor, PP
Comparison groups	PP week 16 - B cell poor Rituximab v PP week 16 - B cell poor Tocilizumab
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.014
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.271
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.058
upper limit	0.485

Statistical analysis title	TOC vs. RTX, B cell rich, PP
Comparison groups	PP week 16 - B cell rich Rituximab v PP week 16 - B cell rich Tocilizumab
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0052
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.327

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.109
upper limit	0.544

Statistical analysis title	TOC vs. RTX, B cell poor (RNA seq), PP
Comparison groups	PP week 16 - B cell poor (RNA_seq) Rituximab v PP week 16 - B cell poor (RNA_seq) Tocilizumab
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0019
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.386
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.166
upper limit	0.607

Statistical analysis title	TOC vs. RTX, B cell rich (RNA seq), PP
Comparison groups	PP week 16 - B cell rich (RNA_seq) RItuximab v PP week 16 - B cell rich (RNA_seq) Tocilizumab
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.066
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.261
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.016
upper limit	0.507

Secondary: DAS28 (CRP) ≤ 2.6

End point title	DAS28 (CRP) ≤ 2.6
End point description:	
End point type	Secondary

End point timeframe:
Timeframe 2: Week 16
Timeframe 3: Week 48

End point values	Rituximab	Tocilizumab	Rituximab	Tocilizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82	79	42	42
Units: Responders				
Responders	12	27	11	24

End point values	ITT week 16 - B cell poor Rituximab	ITT week 16 - B cell poor Tocilizumab	ITT week 16 - B cell rich Rituximab	ITT week 16 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	38	41	33	31
Units: Responders				
Responders	7	13	4	9

End point values	ITT week 16 - B cell poor (RNA_seq) Rituximab	ITT week 16 - B cell poor (RNA_seq) Tocilizumab	ITT week 16 - B cell rich (RNA_seq) Rituximab	ITT week 16 - B cell rich (RNA_seq) Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	32	30	29
Units: Responders				
Responders	4	10	4	8

End point values	PP week 16 - B cell poor Rituximab	PP week 16 - B cell poor Tocilizumab	PP week 16 - B cell rich Rituximab	PP week 16 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	30	31	23
Units: Responders				
Responders	7	11	4	7

End point values	PP week 16 - B cell poor (RNA_seq) Rituximab	PP week 16 - B cell poor (RNA_seq) Tocilizumab	PP week 16 - B cell rich (RNA_seq) Rituximab	PP week 16 - B cell rich (RNA_seq) Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	32	25	28	19

Units: Responders				
Responders	4	9	4	5

End point values	week 24 - B cell poor Rituximab	week 24 - B cell poor Tocilizumab	week 24 - B cell rich Rituximab	week 24 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	21	27	18	20
Units: Responders				
Responders	3	9	2	9

End point values	week 36 - B cell poor Rituximab	week 36 - B cell poor Tocilizumab	week 36 - B cell rich Rituximab	week 36 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	22	17	16
Units: Responders				
Responders	3	9	4	11

End point values	week 48 - B cell poor Rituximab	week 48 - B cell poor Tocilizumab	week 48 - B cell rich Rituximab	week 48 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17	21	17	16
Units: Responders				
Responders	5	11	5	9

Statistical analyses

Statistical analysis title	TOC vs. RTX, B cell poor, ITT
Comparison groups	ITT week 16 - B cell poor Rituximab v ITT week 16 - B cell poor Tocilizumab
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.17
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.133
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.055
upper limit	0.321

Statistical analysis title	TOC vs. RTX, B cell rich, ITT
Comparison groups	ITT week 16 - B cell rich Rituximab v ITT week 16 - B cell rich Tocilizumab
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.169
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.026
upper limit	0.364

Statistical analysis title	TOC vs. RTX, B cell poor (RNA seq), ITT
Comparison groups	ITT week 16 - B cell poor (RNA_seq) Rituximab v ITT week 16 - B cell poor (RNA_seq) Tocilizumab
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.076
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.191
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.387

Statistical analysis title	TOC vs. RTX, B cell rich (RNA seq), ITT
Comparison groups	ITT week 16 - B cell rich (RNA_seq) Rituximab v ITT week 16 - B cell rich (RNA_seq) Tocilizumab
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.21
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.143

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.061
upper limit	0.346

Statistical analysis title	TOC vs. RTX, B cell poor, PP
Comparison groups	PP week 16 - B cell poor Rituximab v PP week 16 - B cell poor Tocilizumab
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.177
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.036
upper limit	0.391

Statistical analysis title	TOC vs. RTX, B cell rich, PP
Comparison groups	PP week 16 - B cell rich Rituximab v PP week 16 - B cell rich Tocilizumab
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.17
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.175
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.047
upper limit	0.397

Statistical analysis title	TOC vs. RTX, B cell poor (RNA seq), PP
Comparison groups	PP week 16 - B cell poor (RNA_seq) Rituximab v PP week 16 - B cell poor (RNA_seq) Tocilizumab

Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.056
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.235
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.015
upper limit	0.455

Statistical analysis title	TOC vs. RTX, B cell rich (RNA seq), PP
Comparison groups	PP week 16 - B cell rich (RNA_seq) RItuximab v PP week 16 - B cell rich (RNA_seq) Tocilizumab
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.45
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.116
upper limit	0.357

Statistical analysis title	TOC vs. RTX, B cell rich (RNA seq), PP
Comparison groups	PP week 16 - B cell rich (RNA_seq) RItuximab v PP week 16 - B cell rich (RNA_seq) Tocilizumab
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.45
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.116
upper limit	0.357

Secondary: Good/Moderate EULAR DAS28 (ESR) response

End point title	Good/Moderate EULAR DAS28 (ESR) response
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End point description:

End point type	Secondary
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End point timeframe:

Timeframe 2: Week 16

Timeframe 3: Week 48

End point values	Rituximab	Tocilizumab	Rituximab	Tocilizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82	79	42	42
Units: Responders				
Responders	60	69	38	39

End point values	ITT week 16 - B cell poor Rituximab	ITT week 16 - B cell poor Tocilizumab	ITT week 16 - B cell rich Rituximab	ITT week 16 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	38	41	33	31
Units: Responders				
Responders	25	36	25	27

End point values	ITT week 16 - B cell poor (RNA_seq) Rituximab	ITT week 16 - B cell poor (RNA_seq) Tocilizumab	ITT week 16 - B cell rich (RNA_seq) Rituximab	ITT week 16 - B cell rich (RNA_seq) Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	32	30	29
Units: Responders				
Responders	21	30	24	24

End point values	PP week 16 - B cell poor Rituximab	PP week 16 - B cell poor Tocilizumab	PP week 16 - B cell rich Rituximab	PP week 16 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	30	31	23
Units: Responders				
Responders	24	29	23	21

End point values	PP week 16 - B cell poor (RNA_seq) Rituximab	PP week 16 - B cell poor (RNA_seq) Tocilizumab	PP week 16 - B cell rich (RNA_seq) Rituximab	PP week 16 - B cell rich (RNA_seq) Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	32	25	28	19
Units: Responders				
Responders	20	25	22	17

End point values	week 24 - B cell poor Rituximab	week 24 - B cell poor Tocilizumab	week 24 - B cell rich Rituximab	week 24 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	21	27	18	20
Units: Responders				
Responders	17	23	14	18

End point values	week 36 - B cell poor Rituximab	week 36 - B cell poor Tocilizumab	week 36 - B cell rich Rituximab	week 36 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	22	17	16
Units: Responders				
Responders	17	22	15	16

End point values	week 48 - B cell poor Rituximab	week 48 - B cell poor Tocilizumab	week 48 - B cell rich Rituximab	week 48 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17	21	17	16
Units: Responders				
Responders	16	21	15	14

Statistical analyses

Statistical analysis title	TOC vs. RTX, B cell poor, ITT
Comparison groups	ITT week 16 - B cell poor Rituximab v ITT week 16 - B cell poor Tocilizumab
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.031
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.22

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.039
upper limit	0.401

Statistical analysis title	TOC vs. RTX, B cell rich, ITT
Comparison groups	ITT week 16 - B cell rich Rituximab v ITT week 16 - B cell rich Tocilizumab
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.34
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.113
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.075
upper limit	0.301

Statistical analysis title	TOC vs. RTX, B cell poor (RNA seq), ITT
Comparison groups	ITT week 16 - B cell poor (RNA_seq) Rituximab v ITT week 16 - B cell poor (RNA_seq) Tocilizumab
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0053
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.301
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.117
upper limit	0.485

Statistical analysis title	TOC vs. RTX, B cell rich (RNA seq), ITT
Comparison groups	ITT week 16 - B cell rich (RNA_seq) Rituximab v ITT week 16 - B cell rich (RNA_seq) Tocilizumab

Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.028
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.171
upper limit	0.226

Statistical analysis title	TOC vs. RTX, B cell poor, PP
Comparison groups	PP week 16 - B cell poor Rituximab v PP week 16 - B cell poor Tocilizumab
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0018
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.318
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.151
upper limit	0.485

Statistical analysis title	TOC vs. RTX, B cell rich, PP
Comparison groups	PP week 16 - B cell rich Rituximab v PP week 16 - B cell rich Tocilizumab
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.16
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.171
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.021
upper limit	0.363

Statistical analysis title	TOC vs. RTX, B cell poor (RNA seq), PP
Comparison groups	PP week 16 - B cell poor (RNA_seq) Rituximab v PP week 16 - B cell poor (RNA_seq) Tocilizumab
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00053
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.375
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.207
upper limit	0.543

Statistical analysis title	TOC vs. RTX, B cell rich (RNA seq), PP
Comparison groups	PP week 16 - B cell rich (RNA_seq) RiItuximab v PP week 16 - B cell rich (RNA_seq) Tocilizumab
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.44
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.109
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.096
upper limit	0.314

Secondary: Good/Moderate EULAR DAS28 (CRP) response	
End point title	Good/Moderate EULAR DAS28 (CRP) response
End point description:	
End point type	Secondary
End point timeframe:	
Timeframe 2: Week 16	
Timeframe 3: Week 48	

End point values	Rituximab	Tocilizumab	Rituximab	Tocilizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82	79	42	42
Units: Responders				
Responders	54	62	34	38

End point values	ITT week 16 - B cell poor Rituximab	ITT week 16 - B cell poor Tocilizumab	ITT week 16 - B cell rich Rituximab	ITT week 16 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	38	41	33	31
Units: Responders				
Responders	22	32	23	25

End point values	ITT week 16 - B cell poor (RNA_seq) Rituximab	ITT week 16 - B cell poor (RNA_seq) Tocilizumab	ITT week 16 - B cell rich (RNA_seq) Rituximab	ITT week 16 - B cell rich (RNA_seq) Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	32	30	29
Units: Responders				
Responders	18	27	23	23

End point values	PP week 16 - B cell poor Rituximab	PP week 16 - B cell poor Tocilizumab	PP week 16 - B cell rich Rituximab	PP week 16 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	30	31	23
Units: Responders				
Responders	21	27	21	18

End point values	PP week 16 - B cell poor (RNA_seq) Rituximab	PP week 16 - B cell poor (RNA_seq) Tocilizumab	PP week 16 - B cell rich (RNA_seq) Rituximab	PP week 16 - B cell rich (RNA_seq) Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	32	25	28	19
Units: Responders				
Responders	17	23	21	15

End point values	week 24 - B cell poor	week 24 - B cell poor	week 24 - B cell rich	week 24 - B cell rich
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	Rituximab	Tocilizumab	Rituximab	Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	21	27	18	20
Units: Responders				
Responders	16	22	14	16

End point values	week 36 - B cell poor Rituximab	week 36 - B cell poor Tocilizumab	week 36 - B cell rich Rituximab	week 36 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	22	17	16
Units: Responders				
Responders	18	22	13	15

End point values	week 48 - B cell poor Rituximab	week 48 - B cell poor Tocilizumab	week 48 - B cell rich Rituximab	week 48 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17	21	17	16
Units: Responders				
Responders	15	20	12	14

Statistical analyses

Statistical analysis title	TOC vs. RTX, B cell poor, ITT
Comparison groups	ITT week 16 - B cell poor Tocilizumab v ITT week 16 - B cell poor Rituximab
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.054
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.202
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.403

Statistical analysis title	TOC vs. RTX, B cell rich, ITT
Comparison groups	ITT week 16 - B cell rich Rituximab v ITT week 16 - B cell rich Tocilizumab

Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.31
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.109
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.319

Statistical analysis title	TOC vs. RTX, B cell poor (RNA seq), ITT
Comparison groups	ITT week 16 - B cell poor (RNA_seq) Rituximab v ITT week 16 - B cell poor (RNA_seq) Tocilizumab
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.298
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.087
upper limit	0.51

Statistical analysis title	TOC vs. RTX, B cell rich (RNA seq), ITT
Comparison groups	ITT week 16 - B cell rich (RNA_seq) Rituximab v ITT week 16 - B cell rich (RNA_seq) Tocilizumab
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.81
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.026
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.185
upper limit	0.238

Statistical analysis title	TOC vs. RTX, B cell poor, PP
Comparison groups	PP week 16 - B cell poor Rituximab v PP week 16 - B cell poor Tocilizumab
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0029
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.332
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.14
upper limit	0.525

Statistical analysis title	TOC vs. RTX, B cell rich, PP
Comparison groups	PP week 16 - B cell rich Rituximab v PP week 16 - B cell rich Tocilizumab
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.54
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.105
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	0.341

Statistical analysis title	TOC vs. RTX, B cell poor (RNA seq), PP
Comparison groups	PP week 16 - B cell poor (RNA_seq) Rituximab v PP week 16 - B cell poor (RNA_seq) Tocilizumab
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0015
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.389
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.186
upper limit	0.592

Statistical analysis title	TOC vs. RTX, B cell rich (RNA seq), PP
Comparison groups	PP week 16 - B cell rich (RNA_seq) RItuximab v PP week 16 - B cell rich (RNA_seq) Tocilizumab
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.039
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.204
upper limit	0.283

Secondary: CDAI, change from baseline

End point title	CDAI, change from baseline
End point description:	
End point type	Secondary
End point timeframe:	
Timeframe 2: Week 16	
Timeframe 3: Week 48	

End point values	Rituximab	Tocilizumab	Rituximab	Tocilizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82	79	42	42
Units: value				
least squares mean (standard deviation)	-13.2 (± 1.3)	-14.8 (± 1.3)	-17.94 (± 1.13)	-22.82 (± 1.13)

End point values	ITT week 16 - B cell poor Rituximab	ITT week 16 - B cell poor Tocilizumab	ITT week 16 - B cell rich Rituximab	ITT week 16 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	38	41	33	31
Units: value				
least squares mean (standard deviation)	-12.1 (± 1.9)	-15.7 (± 1.9)	-13.2 (± 2)	-14.2 (± 2.1)

End point values	ITT week 16 - B cell poor (RNA_seq) Rituximab	ITT week 16 - B cell poor (RNA_seq) Tocilizumab	ITT week 16 - B cell rich (RNA_seq) Rituximab	ITT week 16 - B cell rich (RNA_seq) Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	32	30	29
Units: value				
least squares mean (standard deviation)	-10.9 ($\pm$ 2)	-17.2 ($\pm$ 2)	-14.5 ($\pm$ 2.1)	-14 ($\pm$ 2.1)

End point values	PP week 16 - B cell poor Rituximab	PP week 16 - B cell poor Tocilizumab	PP week 16 - B cell rich Rituximab	PP week 16 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	30	31	23
Units: value				
least squares mean (standard deviation)	-11.9 ($\pm$ 1.9)	-17.9 ($\pm$ 2.1)	-12.8 ($\pm$ 2.1)	-12.6 ($\pm$ 2.4)

End point values	PP week 16 - B cell poor (RNA_seq) Rituximab	PP week 16 - B cell poor (RNA_seq) Tocilizumab	PP week 16 - B cell rich (RNA_seq) Rituximab	PP week 16 - B cell rich (RNA_seq) Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	32	25	28	19
Units: value				
least squares mean (standard deviation)	-10.7 ($\pm$ 2)	-18.6 ($\pm$ 2.2)	-14 ($\pm$ 2.2)	-12.1 ($\pm$ 2.6)

End point values	week 24 - B cell poor Rituximab	week 24 - B cell poor Tocilizumab	week 24 - B cell rich Rituximab	week 24 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	21	27	18	20
Units: value				
least squares mean (standard deviation)	-16.4 ($\pm$ 1.9)	-21.0 ($\pm$ 1.7)	-13.65 ($\pm$ 2.27)	-17.2 ($\pm$ 2.15)

End point values	week 36 - B cell poor Rituximab	week 36 - B cell poor Tocilizumab	week 36 - B cell rich Rituximab	week 36 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	22	17	16
Units: value				
least squares mean (standard deviation)	-17.9 ($\pm$ 1.6)	-22 ($\pm$ 1.5)	-16.8 ($\pm$ 1.78)	-21.8 ($\pm$ 1.83)

End point values	week 48 - B cell poor Rituximab	week 48 - B cell poor Tocilizumab	week 48 - B cell rich Rituximab	week 48 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17	21	17	16
Units: value				
least squares mean (standard deviation)	-20 ($\pm$ 1.55)	-22.8 ($\pm$ 1.4)	-15.61 ($\pm$ 2.06)	-22.51 ($\pm$ 2.12)

Statistical analyses

Statistical analysis title	TOC vs. RTX, B cell poor, ITT
Comparison groups	ITT week 16 - B cell poor Rituximab v ITT week 16 - B cell poor Tocilizumab
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.18
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	8.9

Statistical analysis title	TOC vs. RTX, B cell rich, ITT
Comparison groups	ITT week 16 - B cell rich Rituximab v ITT week 16 - B cell rich Tocilizumab
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.73
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.9
upper limit	6.9

Statistical analysis title	TOC vs. RTX, B cell poor (RNA-seq), ITT
Comparison groups	ITT week 16 - B cell poor (RNA_seq) Rituximab v ITT week 16 - B cell poor (RNA_seq) Tocilizumab
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.029
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	6.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	12

Statistical analysis title	TOC vs. RTX, B cell rich (RNA-seq), ITT
Comparison groups	ITT week 16 - B cell rich (RNA_seq) Rituximab v ITT week 16 - B cell rich (RNA_seq) Tocilizumab
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.88
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.5
upper limit	5.6

Statistical analysis title	TOC vs. RTX, B cell poor, PP
Comparison groups	PP week 16 - B cell poor Rituximab v PP week 16 - B cell poor Tocilizumab
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.043
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	6

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	11.7

Statistical analysis title	TOC vs. RTX, B cell rich, PP
Comparison groups	PP week 16 - B cell rich Rituximab v PP week 16 - B cell rich Tocilizumab
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.93
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.7
upper limit	6.2

Statistical analysis title	TOC vs. RTX, B cell poor (RNA-seq), PP
Comparison groups	PP week 16 - B cell poor (RNA_seq) Rituximab v PP week 16 - B cell poor (RNA_seq) Tocilizumab
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0097
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	7.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	2
upper limit	13.8

Statistical analysis title	TOC vs. RTX, B cell rich (RNA-seq), PP
Comparison groups	PP week 16 - B cell rich (RNA_seq) RItuximab v PP week 16 - B cell rich (RNA_seq) Tocilizumab

Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.58
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.8
upper limit	5

Secondary: DAS28 (ESR), change from baseline

End point title	DAS28 (ESR), change from baseline
End point description:	
End point type	Secondary
End point timeframe:	
Timeframe 2: Week 16	
Timeframe 3: Week 48	

End point values	Rituximab	Tocilizumab	Rituximab	Tocilizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82	79	42	42
Units: value				
least squares mean (standard deviation)	-1.5 (± 0.1)	-2.5 (± 0.1)	-2.14 (± 0.18)	-3.29 (± 0.18)

End point values	ITT week 16 - B cell poor Rituximab	ITT week 16 - B cell poor Tocilizumab	ITT week 16 - B cell rich Rituximab	ITT week 16 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	38	41	33	31
Units: value				
least squares mean (standard deviation)	-1.5 (± 0.2)	-2.6 (± 0.2)	-1.5 (± 0.2)	-2.6 (± 0.2)

End point values	ITT week 16 - B cell poor (RNA_seq) Rituximab	ITT week 16 - B cell poor (RNA_seq) Tocilizumab	ITT week 16 - B cell rich (RNA_seq) Rituximab	ITT week 16 - B cell rich (RNA_seq) Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	32	30	29

Units: value				
least squares mean (standard deviation)	-1.3 ($\pm$ 0.2)	-2.8 ($\pm$ 0.2)	-1.7 ($\pm$ 0.2)	-2.4 ($\pm$ 0.2)

End point values	PP week 16 - B cell poor Rituximab	PP week 16 - B cell poor Tocilizumab	PP week 16 - B cell rich Rituximab	PP week 16 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	30	31	23
Units: value				
least squares mean (standard deviation)	-1.5 ($\pm$ 0.2)	-2.8 ($\pm$ 0.2)	-1.4 ($\pm$ 0.2)	-2.6 ($\pm$ 0.3)

End point values	PP week 16 - B cell poor (RNA_seq) Rituximab	PP week 16 - B cell poor (RNA_seq) Tocilizumab	PP week 16 - B cell rich (RNA_seq) Rituximab	PP week 16 - B cell rich (RNA_seq) Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	32	25	28	19
Units: value				
least squares mean (standard deviation)	-1.3 ($\pm$ 0.2)	-3.0 ($\pm$ 0.3)	-1.7 ($\pm$ 0.2)	-2.4 ($\pm$ 0.3)

End point values	week 24 - B cell poor Rituximab	week 24 - B cell poor Tocilizumab	week 24 - B cell rich Rituximab	week 24 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	21	27	18	20
Units: value				
least squares mean (standard deviation)	-16.4 ($\pm$ 1.9)	-21 ($\pm$ 1.7)	-1.87 ($\pm$ 0.29)	-2.82 ($\pm$ 0.28)

End point values	week 36 - B cell poor Rituximab	week 36 - B cell poor Tocilizumab	week 36 - B cell rich Rituximab	week 36 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	22	17	16
Units: value				
least squares mean (standard deviation)	-17.9 ($\pm$ 1.6)	-22 ($\pm$ 1.5)	-2.26 ($\pm$ 0.25)	-3.39 ($\pm$ 0.26)

End point values	week 48 - B cell poor Rituximab	week 48 - B cell poor Tocilizumab	week 48 - B cell rich Rituximab	week 48 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17	21	17	16
Units: value				

least squares mean (standard deviation)	-20 ($\pm$ 1.55)	-22.8 ($\pm$ 1.4)	-1.98 ($\pm$ 0.34)	-3.39 ($\pm$ 0.35)
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Statistical analyses

Statistical analysis title	TOC vs. RTX, B cell poor, ITT
Comparison groups	ITT week 16 - B cell poor Tocilizumab v ITT week 16 - B cell poor Rituximab
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00063
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.7

Statistical analysis title	TOC vs. RTX, B cell rich, ITT
Comparison groups	ITT week 16 - B cell rich Rituximab v ITT week 16 - B cell rich Tocilizumab
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00088
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.7

Statistical analysis title	TOC vs. RTX, B cell poor (RNA seq), ITT
Comparison groups	ITT week 16 - B cell poor (RNA_seq) Rituximab v ITT week 16 - B cell poor (RNA_seq) Tocilizumab

Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.000012
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	2.2

Statistical analysis title	TOC vs. RTX, B cell rich (RNA seq), ITT
Comparison groups	ITT week 16 - B cell rich (RNA_seq) Rituximab v ITT week 16 - B cell rich (RNA_seq) Tocilizumab
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.026
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	1.4

Statistical analysis title	TOC vs. RTX, B cell poor, PP
Comparison groups	PP week 16 - B cell poor Rituximab v PP week 16 - B cell poor Tocilizumab
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.000053
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	2

Statistical analysis title	TOC vs. RTX, B cell rich, PP
Comparison groups	PP week 16 - B cell rich Rituximab v PP week 16 - B cell rich Tocilizumab
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00095
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.9

Statistical analysis title	TOC vs. RTX, B cell poor (RNA seq), PP
Comparison groups	PP week 16 - B cell poor (RNA_seq) Rituximab v PP week 16 - B cell poor (RNA_seq) Tocilizumab
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.000004
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	2.4

Statistical analysis title	TOC vs. RTX, B cell rich (RNA seq), PP
Comparison groups	PP week 16 - B cell rich (RNA_seq) Rituximab v PP week 16 - B cell rich (RNA_seq) Tocilizumab
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	1.5

Secondary: DAS28 (CRP), change from baseline

End point title	DAS28 (CRP), change from baseline
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End point description:

End point type	Secondary
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End point timeframe:

Timeframe 2: Week 16

Timeframe 3: Week 48

End point values	Rituximab	Tocilizumab	Rituximab	Tocilizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82	79	42	42
Units: value				
least squares mean (standard deviation)	-1.4 (± 0.1)	-2 (± 0.1)	-1.82 (± 0.15)	-2.7 (± 0.15)

End point values	ITT week 16 - B cell poor Rituximab	ITT week 16 - B cell poor Tocilizumab	ITT week 16 - B cell rich Rituximab	ITT week 16 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	38	41	33	31
Units: value				
least squares mean (standard deviation)	-1.3 (± 0.2)	-2.0 (± 0.2)	-1.5 (± 0.2)	-2.0 (± 0.2)

End point values	ITT week 16 - B cell poor (RNA_seq) Rituximab	ITT week 16 - B cell poor (RNA_seq) Tocilizumab	ITT week 16 - B cell rich (RNA_seq) Rituximab	ITT week 16 - B cell rich (RNA_seq) Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	32	30	29
Units: value				
least squares mean (standard deviation)	-1.1 (± 0.2)	-2.1 (± 0.2)	-1.6 (± 0.2)	-1.9 (± 0.2)

End point values	PP week 16 - B cell poor Rituximab	PP week 16 - B cell poor Tocilizumab	PP week 16 - B cell rich Rituximab	PP week 16 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	30	31	23
Units: value				
least squares mean (standard deviation)	-1.3 (± 0.2)	-2.2 (± 0.2)	-1.4 (± 0.2)	-2.0 (± 0.2)

End point values	PP week 16 - B cell poor (RNA_seq) Rituximab	PP week 16 - B cell poor (RNA_seq) Tocilizumab	PP week 16 - B cell rich (RNA_seq) Rituximab	PP week 16 - B cell rich (RNA_seq) Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	32	25	28	19
Units: value				
least squares mean (standard deviation)	-1.1 (± 0.2)	-2.3 (± 0.2)	-1.6 (± 0.2)	-1.8 (± 0.3)

End point values	week 24 - B cell poor Rituximab	week 24 - B cell poor Tocilizumab	week 24 - B cell rich Rituximab	week 24 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	21	27	18	20
Units: value				
least squares mean (standard deviation)	-1.6 (± 0.26)	-2.33 (± 0.23)	-1.64 (± 0.29)	-2.15 (± 0.27)

End point values	week 36 - B cell poor Rituximab	week 36 - B cell poor Tocilizumab	week 36 - B cell rich Rituximab	week 36 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	22	17	16
Units: value				
least squares mean (standard deviation)	-1.98 (± 0.19)	-2.6 (± 0.19)	-1.88 (± 0.22)	-2.72 (± 0.22)

End point values	week 48 - B cell poor Rituximab	week 48 - B cell poor Tocilizumab	week 48 - B cell rich Rituximab	week 48 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17	21	17	16
Units: value				
least squares mean (standard deviation)	-2.03 (± 0.23)	-2.64 (± 0.21)	-1.76 (± 0.26)	-2.73 (± 0.27)

Statistical analyses

Statistical analysis title	TOC vs. RTX, B cell poor, ITT
Comparison groups	ITT week 16 - B cell poor Rituximab v ITT week 16 - B cell poor Tocilizumab

Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.032
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	1.3

Statistical analysis title	TOC vs. RTX, B cell rich, ITT
Comparison groups	ITT week 16 - B cell rich Rituximab v ITT week 16 - B cell rich Tocilizumab
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.059
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	1.1

Statistical analysis title	TOC vs. RTX, B cell poor (RNA seq), ITT
Comparison groups	ITT week 16 - B cell poor (RNA_seq) Rituximab v ITT week 16 - B cell poor (RNA_seq) Tocilizumab
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0021
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	1.6

Statistical analysis title	TOC vs. RTX, B cell rich (RNA seq), ITT
Comparison groups	ITT week 16 - B cell rich (RNA_seq) Rituximab v ITT week 16 - B cell rich (RNA_seq) Tocilizumab
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.34
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.9

Statistical analysis title	TOC vs. RTX, B cell poor, PP
Comparison groups	PP week 16 - B cell poor Rituximab v PP week 16 - B cell poor Tocilizumab
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0054
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	1.5

Statistical analysis title	TOC vs. RTX, B cell rich, PP
Comparison groups	PP week 16 - B cell rich Rituximab v PP week 16 - B cell rich Tocilizumab
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.076
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	1.2

Statistical analysis title	TOC vs. RTX, B cell poor (RNA seq), PP
Comparison groups	PP week 16 - B cell poor (RNA_seq) Rituximab v PP week 16 - B cell poor (RNA_seq) Tocilizumab
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00033
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.9

Statistical analysis title	TOC vs. RTX, B cell rich (RNA seq), PP
Comparison groups	PP week 16 - B cell rich (RNA_seq) RItuximab v PP week 16 - B cell rich (RNA_seq) Tocilizumab
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.47
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.9

Secondary: HAQ score, change from baseline

End point title	HAQ score, change from baseline
End point description:	
End point type	Secondary
End point timeframe:	
Timeframe 2: Week 16	
Timeframe 3: Week 48	

End point values	Rituximab	Tocilizumab	Rituximab	Tocilizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82	79	42	42
Units: value				
least squares mean (standard deviation)	-0.3 (± 0.1)	-0.4 (± 0.1)	-0.44 (± 0.1)	-0.66 (± 0.09)

End point values	ITT week 16 - B cell poor Rituximab	ITT week 16 - B cell poor Tocilizumab	ITT week 16 - B cell rich Rituximab	ITT week 16 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	38	41	33	31
Units: value				
least squares mean (standard deviation)	-0.3 (± 0.1)	-0.4 (± 0.1)	-0.3 (± 0.1)	-0.4 (± 0.1)

End point values	ITT week 16 - B cell poor (RNA_seq) Rituximab	ITT week 16 - B cell poor (RNA_seq) Tocilizumab	ITT week 16 - B cell rich (RNA_seq) Rituximab	ITT week 16 - B cell rich (RNA_seq) Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	32	30	29
Units: value				
least squares mean (standard deviation)	-0.2 (± 0.1)	-0.2 (± 0.1)	-0.3 (± 0.1)	-0.5 (± 0.1)

End point values	PP week 16 - B cell poor Rituximab	PP week 16 - B cell poor Tocilizumab	PP week 16 - B cell rich Rituximab	PP week 16 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	30	31	23
Units: value				
least squares mean (standard deviation)	-0.3 (± 0.1)	-0.4 (± 0.1)	-0.3 (± 0.1)	-0.3 (± 0.1)

End point values	PP week 16 - B cell poor (RNA_seq) Rituximab	PP week 16 - B cell poor (RNA_seq) Tocilizumab	PP week 16 - B cell rich (RNA_seq) Rituximab	PP week 16 - B cell rich (RNA_seq) Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	32	25	28	19
Units: value				
least squares mean (standard deviation)	-0.2 (± 0.1)	-0.2 (± 0.1)	-0.3 (± 0.1)	-0.4 (± 0.1)

End point values	week 24 - B cell poor	week 24 - B cell poor	week 24 - B cell rich	week 24 - B cell rich
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	Rituximab	Tocilizumab	Rituximab	Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	21	27	18	20
Units: value				
least squares mean (standard deviation)	-0.25 ($\pm$ 0.14)	-0.45 ($\pm$ 0.12)	-0.47 ($\pm$ 0.11)	-0.38 ($\pm$ 0.11)

End point values	week 36 - B cell poor Rituximab	week 36 - B cell poor Tocilizumab	week 36 - B cell rich Rituximab	week 36 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	22	17	16
Units: value				
least squares mean (standard deviation)	-0.35 ($\pm$ 0.13)	-0.65 ($\pm$ 0.12)	-0.59 ($\pm$ 0.14)	-0.55 ($\pm$ 0.14)

End point values	week 48 - B cell poor Rituximab	week 48 - B cell poor Tocilizumab	week 48 - B cell rich Rituximab	week 48 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17	21	17	16
Units: value				
least squares mean (standard deviation)	-0.41 ($\pm$ 0.14)	0.65 ($\pm$ 0.13)	-0.58 ($\pm$ 0.16)	-0.64 ($\pm$ 0.16)

Statistical analyses

Statistical analysis title	TOC vs. RTX, B cell poor, ITT
Comparison groups	ITT week 16 - B cell poor Rituximab v ITT week 16 - B cell poor Tocilizumab
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.3

Statistical analysis title	TOC vs. RTX, B cell rich, ITT
Comparison groups	ITT week 16 - B cell rich Rituximab v ITT week 16 - B cell rich Tocilizumab

Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.41
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.4

Statistical analysis title	TOC vs. RTX, B cell poor (RNA seq), ITT
Comparison groups	ITT week 16 - B cell poor (RNA_seq) Rituximab v ITT week 16 - B cell poor (RNA_seq) Tocilizumab
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.91
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.2

Statistical analysis title	TOC vs. RTX, B cell rich (RNA seq), ITT
Comparison groups	ITT week 16 - B cell rich (RNA_seq) Rituximab v ITT week 16 - B cell rich (RNA_seq) Tocilizumab
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.085
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.5

Statistical analysis title	TOC vs. RTX, B cell poor, PP
Comparison groups	PP week 16 - B cell poor Rituximab v PP week 16 - B cell poor Tocilizumab
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.26
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.4

Statistical analysis title	TOC vs. RTX, B cell rich, PP
Comparison groups	PP week 16 - B cell rich Rituximab v PP week 16 - B cell rich Tocilizumab
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.88
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.3

Statistical analysis title	TOC vs. RTX, B cell poor (RNA seq), PP
Comparison groups	PP week 16 - B cell poor (RNA_seq) Rituximab v PP week 16 - B cell poor (RNA_seq) Tocilizumab
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.86
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.3

Statistical analysis title	TOC vs. RTX, B cell rich (RNA seq), PP
Comparison groups	PP week 16 - B cell rich (RNA_seq) RItuximab v PP week 16 - B cell rich (RNA_seq) Tocilizumab
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.24
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.4

Secondary: FACIT score, change from baseline

End point title	FACIT score, change from baseline
End point description:	
End point type	Secondary
End point timeframe:	
Timeframe 2: Week 16	
Timeframe 3: Week 48	

End point values	Rituximab	Tocilizumab	Rituximab	Tocilizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82	79	42	42
Units: values				
least squares mean (standard deviation)	4.6 (± 1)	6.7 (± 1)	7.5 (± 1.5)	8.3 (± 1.5)

End point values	ITT week 16 - B cell poor Rituximab	ITT week 16 - B cell poor Tocilizumab	ITT week 16 - B cell rich Rituximab	ITT week 16 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	38	41	33	31
Units: values				
least squares mean (standard deviation)	1.6 (± 1.1)	5.6 (± 1.1)	8.5 (± 1.9)	7.8 (± 2.0)

End point values	ITT week 16 - B cell poor (RNA_seq) Rituximab	ITT week 16 - B cell poor (RNA_seq) Tocilizumab	ITT week 16 - B cell rich (RNA_seq) Rituximab	ITT week 16 - B cell rich (RNA_seq) Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	32	30	29
Units: values				
least squares mean (standard deviation)	2.1 ($\pm$ 1.4)	4.9 ($\pm$ 1.4)	6.9 ($\pm$ 1.8)	8.3 ($\pm$ 1.9)

End point values	PP week 16 - B cell poor Rituximab	PP week 16 - B cell poor Tocilizumab	PP week 16 - B cell rich Rituximab	PP week 16 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	30	31	23
Units: values				
least squares mean (standard deviation)	1.7 ($\pm$ 1.1)	5.6 ($\pm$ 1.2)	7.8 ($\pm$ 1.9)	7.4 ($\pm$ 2.2)

End point values	PP week 16 - B cell poor (RNA_seq) Rituximab	PP week 16 - B cell poor (RNA_seq) Tocilizumab	PP week 16 - B cell rich (RNA_seq) Rituximab	PP week 16 - B cell rich (RNA_seq) Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	32	25	28	19
Units: values				
least squares mean (standard deviation)	2.3 ($\pm$ 1.4)	4.2 ($\pm$ 1.6)	6.0 ($\pm$ 1.7)	8.1 ($\pm$ 2.0)

End point values	week 24 - B cell poor Rituximab	week 24 - B cell poor Tocilizumab	week 24 - B cell rich Rituximab	week 24 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	21	27	18	20
Units: values				
least squares mean (standard deviation)	1.95 ($\pm$ 1.8)	6.6 ($\pm$ 1.65)	10.3 ($\pm$ 2.1)	6.2 ($\pm$ 2)

End point values	week 36 - B cell poor Rituximab	week 36 - B cell poor Tocilizumab	week 36 - B cell rich Rituximab	week 36 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	22	17	16
Units: values				
least squares mean (standard deviation)	5.08 ($\pm$ 1.85)	7.84 ($\pm$ 1.76)	14.0 ($\pm$ 2.1)	8.1 ($\pm$ 2.1)

End point values	week 48 - B cell poor Rituximab	week 48 - B cell poor Tocilizumab	week 48 - B cell rich Rituximab	week 48 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17	21	17	16
Units: values				
least squares mean (standard deviation)	5.58 ($\pm$ 2.2)	7.11 ($\pm$ 2)	11.4 ($\pm$ 2.8)	8.4 ($\pm$ 2.86)

Statistical analyses

Statistical analysis title	TOC vs. RTX, B cell poor, ITT
Comparison groups	ITT week 16 - B cell poor Tocilizumab v ITT week 16 - B cell poor Rituximab
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.2
upper limit	-0.8

Statistical analysis title	TOC vs. RTX, B cell rich, ITT
Comparison groups	ITT week 16 - B cell rich Rituximab v ITT week 16 - B cell rich Tocilizumab
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.79
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.8
upper limit	6.3

Statistical analysis title	TOC vs. RTX, B cell poor (RNA seq), ITT
Comparison groups	ITT week 16 - B cell poor (RNA_seq) Rituximab v ITT week 16 - B cell poor (RNA_seq) Tocilizumab
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.16
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.8
upper limit	1.2

Statistical analysis title	TOC vs. RTX, B cell rich (RNA seq), ITT
Comparison groups	ITT week 16 - B cell rich (RNA_seq) Rituximab v ITT week 16 - B cell rich (RNA_seq) Tocilizumab
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.58
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.6
upper limit	3.8

Statistical analysis title	TOC vs. RTX, B cell poor, PP
Comparison groups	PP week 16 - B cell poor Rituximab v PP week 16 - B cell poor Tocilizumab
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.021
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7
upper limit	-0.6

Statistical analysis title	TOC vs. RTX, B cell rich, PP
Comparison groups	PP week 16 - B cell rich Rituximab v PP week 16 - B cell rich Tocilizumab
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.92
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.6
upper limit	6.2

Statistical analysis title	TOC vs. RTX, B cell poor (RNA seq), PP
Comparison groups	PP week 16 - B cell poor (RNA_seq) Rituximab v PP week 16 - B cell poor (RNA_seq) Tocilizumab
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.37
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.2
upper limit	2.4

Statistical analysis title	TOC vs. RTX, B cell rich (RNA seq), PP
Comparison groups	PP week 16 - B cell rich (RNA_seq) Rituximab v PP week 16 - B cell rich (RNA_seq) Tocilizumab
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.44
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.5
upper limit	3.3

Secondary: Ultrasound synovial Thickness 12-max score, change from baseline

End point title	Ultrasound synovial Thickness 12-max score, change from baseline
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End point description:

End point type	Secondary
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End point timeframe:

Timeframe 2: Week 16

Timeframe 3: Week 48

End point values	Rituximab	Tocilizumab	Rituximab	Tocilizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82	79	42	42
Units: values				
least squares mean (standard deviation)	-0.5 (± 0.9)	-1 (± 1)	-2.16 (± 1.25)	-1.37 (± 1.25)

End point values	ITT week 16 - B cell poor Rituximab	ITT week 16 - B cell poor Tocilizumab	ITT week 16 - B cell rich Rituximab	ITT week 16 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	38	41	33	31
Units: values				
least squares mean (standard deviation)	-0.2 (± 1.5)	0.4 (± 1.6)	-0.8 (± 1.1)	-2.5 (± 1.2)

End point values	ITT week 16 - B cell poor (RNA_seq) Rituximab	ITT week 16 - B cell poor (RNA_seq) Tocilizumab	ITT week 16 - B cell rich (RNA_seq) Rituximab	ITT week 16 - B cell rich (RNA_seq) Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	32	30	29
Units: values				
least squares mean (standard deviation)	-1.4 (± 1.7)	2.2 (± 1.7)	-0.5 (± 1.0)	-4.1 (± 1.2)

End point values	PP week 16 - B	PP week 16 - B	PP week 16 - B	PP week 16 - B
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	cell poor Rituximab	cell poor Tocilizumab	cell rich Rituximab	cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	30	31	23
Units: values				
least squares mean (standard deviation)	-0.4 (± 1.5)	-1.3 (± 1.8)	-0.9 (± 1.2)	-2.6 (± 1.3)

End point values	PP week 16 - B cell poor (RNA_seq) Rituximab	PP week 16 - B cell poor (RNA_seq) Tocilizumab	PP week 16 - B cell rich (RNA_seq) Rituximab	PP week 16 - B cell rich (RNA_seq) Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	32	25	28	19
Units: values				
least squares mean (standard deviation)	-1.6 (± 1.8)	1.0 (± 2.0)	-0.5 (± 1.0)	-4.8 (± 1.4)

End point values	week 48 - B cell poor Rituximab	week 48 - B cell poor Tocilizumab	week 48 - B cell rich Rituximab	week 48 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17	21	17	16
Units: values				
least squares mean (standard deviation)	-2.16 (± 2.43)	2.62 (± 2.88)	2.32 (± 1.63)	3.35 (± 1.63)

Statistical analyses

Statistical analysis title	TOC vs RTX, B cell poor, ITT
Comparison groups	ITT week 16 - B cell poor Rituximab v ITT week 16 - B cell poor Tocilizumab
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.82
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.1
upper limit	4.1

Statistical analysis title	TOC vs RTX, B cell rich, ITT
Comparison groups	ITT week 16 - B cell rich Rituximab v ITT week 16 - B cell rich

	Tocilizumab
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.33
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	5

Statistical analysis title	TOC vs RTX, B cell poor (RNA seq), ITT
Comparison groups	ITT week 16 - B cell poor (RNA_seq) Rituximab v ITT week 16 - B cell poor (RNA_seq) Tocilizumab
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.16
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.7
upper limit	1.6

Statistical analysis title	TOC vs RTX, B cell rich (RNA seq), ITT
Comparison groups	ITT week 16 - B cell rich (RNA_seq) Rituximab v ITT week 16 - B cell rich (RNA_seq) Tocilizumab
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.037
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	6.9

Statistical analysis title	TOC vs RTX, B cell poor, PP
Comparison groups	PP week 16 - B cell poor Rituximab v PP week 16 - B cell poor Tocilizumab
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.72
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.2
upper limit	5.9

Statistical analysis title	TOC vs RTX, B cell rich, PP
Comparison groups	PP week 16 - B cell rich Rituximab v PP week 16 - B cell rich Tocilizumab
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.36
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	5.4

Statistical analysis title	TOC vs RTX, B cell poor (RNA seq), PP
Comparison groups	PP week 16 - B cell poor (RNA_seq) Rituximab v PP week 16 - B cell poor (RNA_seq) Tocilizumab
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.33
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.3
upper limit	2.9

Statistical analysis title	TOC vs RTX, B cell rich (RNA seq), PP
Comparison groups	PP week 16 - B cell rich (RNA_seq) RItuximab v PP week 16 - B cell rich (RNA_seq) Tocilizumab
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	4.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	8.1

Secondary: SF36 - Physical Component Summary

End point title	SF36 - Physical Component Summary
End point description:	
End point type	Secondary
End point timeframe:	
Timeframe 2: Week 16	
Timeframe 3: Week 48	

End point values	Rituximab	Tocilizumab	Rituximab	Tocilizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82	79	42	42
Units: values				
least squares mean (standard deviation)	4.9 (± 1.1)	8.3 (± 1.2)	9.4 (± 1.6)	15.3 (± 1.7)

End point values	ITT week 16 - B cell poor Rituximab	ITT week 16 - B cell poor Tocilizumab	ITT week 16 - B cell rich Rituximab	ITT week 16 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	38	41	33	31

Units: values				
least squares mean (standard deviation)	4.0 (± 1.5)	7.3 (± 1.5)	7.0 (± 1.9)	8.5 (± 2.1)

End point values	ITT week 16 - B cell poor (RNA_seq) Rituximab	ITT week 16 - B cell poor (RNA_seq) Tocilizumab	ITT week 16 - B cell rich (RNA_seq) Rituximab	ITT week 16 - B cell rich (RNA_seq) Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	32	30	29
Units: values				
least squares mean (standard deviation)	3.5 (± 1.5)	4.3 (± 1.5)	6.9 (± 1.9)	10.9 (± 2.1)

End point values	PP week 16 - B cell poor Rituximab	PP week 16 - B cell poor Tocilizumab	PP week 16 - B cell rich Rituximab	PP week 16 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	30	31	23
Units: values				
least squares mean (standard deviation)	4.3 (± 1.5)	8.3 (± 1.7)	6.3 (± 1.8)	6.4 (± 2.1)

End point values	PP week 16 - B cell poor (RNA_seq) Rituximab	PP week 16 - B cell poor (RNA_seq) Tocilizumab	PP week 16 - B cell rich (RNA_seq) Rituximab	PP week 16 - B cell rich (RNA_seq) Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	32	25	28	19
Units: values				
least squares mean (standard deviation)	3.7 (± 1.5)	4.2 (± 1.7)	6.2 (± 1.8)	8.9 (± 2.1)

End point values	week 24 - B cell poor Rituximab	week 24 - B cell poor Tocilizumab	week 24 - B cell rich Rituximab	week 24 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	21	27	18	20
Units: values				
least squares mean (standard deviation)	7.7 (± 2)	8.73 (± 1.94)	11.7 (± 2.4)	10 (± 2.34)

End point values	week 36 - B cell poor Rituximab	week 36 - B cell poor Tocilizumab	week 36 - B cell rich Rituximab	week 36 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	22	17	16

Units: values				
least squares mean (standard deviation)	7.96 (± 2.36)	13.3 (± 2.3)	11.2 (± 2.95)	10.16 (± 2.95)

End point values	week 48 - B cell poor Rituximab	week 48 - B cell poor Tocilizumab	week 48 - B cell rich Rituximab	week 48 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17	21	17	16
Units: values				
least squares mean (standard deviation)	8.6 (± 2.5)	16.2 (± 2.4)	10.22 (± 2.98)	13.27 (± 2.07)

Statistical analyses

Statistical analysis title	TOC vs. RTX, B cell poor, ITT
Comparison groups	ITT week 16 - B cell poor Tocilizumab v ITT week 16 - B cell poor Rituximab
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.4
upper limit	0.9

Statistical analysis title	TOC vs. RTX, B cell rich, ITT
Comparison groups	ITT week 16 - B cell rich Rituximab v ITT week 16 - B cell rich Tocilizumab
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.59
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.2
upper limit	4.1

Statistical analysis title	TOC vs. RTX, B cell poor (RNA seq), ITT
Comparison groups	ITT week 16 - B cell poor (RNA_seq) Rituximab v ITT week 16 - B cell poor (RNA_seq) Tocilizumab
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.72
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	3.4

Statistical analysis title	TOC vs. RTX, B cell rich (RNA seq), ITT
Comparison groups	ITT week 16 - B cell rich (RNA_seq) Rituximab v ITT week 16 - B cell rich (RNA_seq) Tocilizumab
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.16
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.6
upper limit	1.6

Statistical analysis title	TOC vs. RTX, B cell poor, PP
Comparison groups	PP week 16 - B cell poor Rituximab v PP week 16 - B cell poor Tocilizumab
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.08
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.5
upper limit	0.5

Statistical analysis title	TOC vs. RTX, B cell rich, PP
Comparison groups	PP week 16 - B cell rich Rituximab v PP week 16 - B cell rich Tocilizumab
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.98
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.7
upper limit	5.5

Statistical analysis title	TOC vs. RTX, B cell poor (RNA seq), PP
Comparison groups	PP week 16 - B cell poor (RNA_seq) Rituximab v PP week 16 - B cell poor (RNA_seq) Tocilizumab
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.83
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.1
upper limit	4.1

Statistical analysis title	TOC vs. RTX, B cell rich (RNA seq), PP
Comparison groups	PP week 16 - B cell rich (RNA_seq) RItuximab v PP week 16 - B cell rich (RNA_seq) Tocilizumab

Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.33
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.2
upper limit	2.8

Secondary: SF36 - Mental Component Summary

End point title	SF36 - Mental Component Summary
End point description:	
End point type	Secondary
End point timeframe:	
Timeframe 2: Week 16	
Timeframe 3: Week 48	

End point values	Rituximab	Tocilizumab	Rituximab	Tocilizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82	79	42	42
Units: values				
least squares mean (standard deviation)	1.7 (± 1.2)	3.2 (± 1.3)	4.54 (± 1.66)	4.78 (± 1.7)

End point values	ITT week 16 - B cell poor Rituximab	ITT week 16 - B cell poor Tocilizumab	ITT week 16 - B cell rich Rituximab	ITT week 16 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	38	41	33	31
Units: values				
least squares mean (standard deviation)	-0.7 (± 1.6)	2.1 (± 1.6)	5.4 (± 2.2)	3.3 (± 2.4)

End point values	ITT week 16 - B cell poor (RNA_seq) Rituximab	ITT week 16 - B cell poor (RNA_seq) Tocilizumab	ITT week 16 - B cell rich (RNA_seq) Rituximab	ITT week 16 - B cell rich (RNA_seq) Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	32	30	29

Units: values				
least squares mean (standard deviation)	0.9 (± 1.8)	4.5 (± 1.8)	4.4 (± 2.3)	3.0 (± 2.5)

End point values	PP week 16 - B cell poor Rituximab	PP week 16 - B cell poor Tocilizumab	PP week 16 - B cell rich Rituximab	PP week 16 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	30	31	23
Units: values				
least squares mean (standard deviation)	-0.7 (± 1.6)	2.7 (± 1.8)	4.4 (± 2.3)	4.2 (± 2.6)

End point values	PP week 16 - B cell poor (RNA_seq) Rituximab	PP week 16 - B cell poor (RNA_seq) Tocilizumab	PP week 16 - B cell rich (RNA_seq) Rituximab	PP week 16 - B cell rich (RNA_seq) Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	32	25	28	19
Units: values				
least squares mean (standard deviation)	1.0 (± 1.8)	5.1 (± 2.1)	3.1 (± 2.3)	4.2 (± 2.8)

End point values	week 24 - B cell poor Rituximab	week 24 - B cell poor Tocilizumab	week 24 - B cell rich Rituximab	week 24 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	21	27	18	20
Units: values				
least squares mean (standard deviation)	-2.66 (± 2.86)	3.91 (± 2.67)	2.53 (± 2.69)	5.7 (± 2.61)

End point values	week 36 - B cell poor Rituximab	week 36 - B cell poor Tocilizumab	week 36 - B cell rich Rituximab	week 36 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	22	17	16
Units: values				
least squares mean (standard deviation)	-0.98 (± 2.2)	3.82 (± 2.15)	7.1 (± 2.36)	3.25 (± 2.36)

End point values	week 48 - B cell poor Rituximab	week 48 - B cell poor Tocilizumab	week 48 - B cell rich Rituximab	week 48 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17	21	17	16
Units: values				

least squares mean (standard deviation)	1.54 ($\pm$ 2.7)	4.7 ($\pm$ 2.54)	7.75 ($\pm$ 2.68)	3.37 ($\pm$ 2.77)
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Statistical analyses

Statistical analysis title	TOC vs. RTX, B cell poor, ITT
Comparison groups	ITT week 16 - B cell poor Rituximab v ITT week 16 - B cell poor Tocilizumab
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.22
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.3
upper limit	1.7

Statistical analysis title	TOC vs. RTX, B cell rich, ITT
Comparison groups	ITT week 16 - B cell rich Rituximab v ITT week 16 - B cell rich Tocilizumab
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.53
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	8.5

Statistical analysis title	TOC vs. RTX, B cell poor (RNA seq), ITT
Comparison groups	ITT week 16 - B cell poor (RNA_seq) Rituximab v ITT week 16 - B cell poor (RNA_seq) Tocilizumab

Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.16
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.8
upper limit	1.5

Statistical analysis title	TOC vs. RTX, B cell rich (RNA seq), ITT
Comparison groups	ITT week 16 - B cell rich (RNA_seq) Rituximab v ITT week 16 - B cell rich (RNA_seq) Tocilizumab
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.68
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.4
upper limit	8.2

Statistical analysis title	TOC vs. RTX, B cell poor, PP
Comparison groups	PP week 16 - B cell poor Rituximab v PP week 16 - B cell poor Tocilizumab
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.16
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.1
upper limit	1.4

Statistical analysis title	TOC vs. RTX, B cell rich, PP
Comparison groups	PP week 16 - B cell rich Rituximab v PP week 16 - B cell rich Tocilizumab
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.96
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.7
upper limit	7.1

Statistical analysis title	TOC vs. RTX, B cell poor (RNA seq), PP
Comparison groups	PP week 16 - B cell poor (RNA_seq) Rituximab v PP week 16 - B cell poor (RNA_seq) Tocilizumab
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.14
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.6
upper limit	1.4

Statistical analysis title	TOC vs. RTX, B cell rich (RNA seq), PP
Comparison groups	PP week 16 - B cell rich (RNA_seq) Rituximab v PP week 16 - B cell rich (RNA_seq) Tocilizumab
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.78
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.4
upper limit	6.3

Secondary: SHSS total score, change from baseline

End point title	SHSS total score, change from baseline
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End point description:

End point type	Secondary
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End point timeframe:

Week 24

Week 48

End point values	week 24 - B cell poor Rituximab	week 24 - B cell poor Tocilizumab	week 24 - B cell rich Rituximab	week 24 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	21	27	18	20
Units: score				
least squares mean (standard deviation)	0.09 (± 0.58)	1.2 (± 0.43)	0.36 (± 0.21)	0.31 (± 0.19)

End point values	week 48 - B cell poor Rituximab	week 48 - B cell poor Tocilizumab	week 48 - B cell rich Rituximab	week 48 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17	21	17	16
Units: score				
least squares mean (standard deviation)	0.02 (± 0.69)	1.15 (± 0.56)	0.36 (± 0.2)	0.25 (± 0.21)

Statistical analyses

Statistical analysis title	TOC vs. RTX, B cell poor, week 24
Comparison groups	week 24 - B cell poor Rituximab v week 24 - B cell poor Tocilizumab
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.61
upper limit	0.38

Statistical analysis title	TOC vs. RTX, B cell rich, week 24
Comparison groups	week 24 - B cell rich Rituximab v week 24 - B cell rich Tocilizumab
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.52
upper limit	0.64

Statistical analysis title	TOC vs. RTX, B cell rich, week 48
Comparison groups	week 48 - B cell rich Rituximab v week 48 - B cell rich Tocilizumab
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.51
upper limit	0.73

Statistical analysis title	TOC vs. RTX, B cell poor, week 48
Comparison groups	week 48 - B cell poor Tocilizumab v week 48 - B cell poor Rituximab
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.14

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.02
upper limit	0.75

Secondary: SHSS Erosion score, change from baseline

End point title	SHSS Erosion score, change from baseline
End point description:	
End point type	Secondary
End point timeframe:	
Week 24	
Week 48	

End point values	week 24 - B cell poor Rituximab	week 24 - B cell poor Tocilizumab	week 24 - B cell rich Rituximab	week 24 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	21	27	18	20
Units: score				
arithmetic mean (standard deviation)	0.13 (± 0.24)	0.39 (± 0.18)	0.36 (± 0.16)	0.04 (± 0.15)

End point values	week 48 - B cell poor Rituximab	week 48 - B cell poor Tocilizumab	week 48 - B cell rich Rituximab	week 48 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17	21	17	16
Units: score				
arithmetic mean (standard deviation)	0.08 (± 0.29)	0.32 (± 0.24)	0.36 (± 0.18)	0.05 (± 0.19)

Statistical analyses

Statistical analysis title	TOC vs. RTX, B cell poor, week 24
Comparison groups	week 24 - B cell poor Rituximab v week 24 - B cell poor Tocilizumab
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.26

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.89
upper limit	0.37

Statistical analysis title	TOC vs. RTX, B cell poor, week 48
Comparison groups	week 48 - B cell poor Rituximab v week 48 - B cell poor Tocilizumab
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.04
upper limit	0.55

Statistical analysis title	TOC vs. RTX, B cell rich, week 24
Comparison groups	week 24 - B cell rich Rituximab v week 24 - B cell rich Tocilizumab
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	0.79

Statistical analysis title	TOC vs. RTX, B cell rich, week 48
Comparison groups	week 48 - B cell rich Rituximab v week 48 - B cell rich Tocilizumab

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	0.85

Secondary: SHSS Joint Space Narrowing score

End point title	SHSS Joint Space Narrowing score
End point description:	
End point type	Secondary
End point timeframe:	
Week 24	
Week 48	

End point values	week 24 - B cell poor Rituximab	week 24 - B cell poor Tocilizumab	week 24 - B cell rich Rituximab	week 24 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	21	27	18	20
Units: score				
arithmetic mean (standard deviation)	-0.08 (± 0.37)	0.61 (± 0.28)	0.23 (± 0.19)	0.23 (± 0.17)

End point values	week 48 - B cell poor Rituximab	week 48 - B cell poor Tocilizumab	week 48 - B cell rich Rituximab	week 48 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17	21	17	16
Units: score				
arithmetic mean (standard deviation)	-0.12 (± 0.44)	0.58 (± 0.35)	0.22 (± 0.2)	0.2 (± 0.21)

Statistical analyses

Statistical analysis title	TOC vs. RTX, B cell poor, week 24
Comparison groups	week 24 - B cell poor Rituximab v week 24 - B cell poor Tocilizumab

Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.65
upper limit	0.28

Statistical analysis title	TOC vs. RTX, B cell poor, week 48
Comparison groups	week 48 - B cell poor Rituximab v week 48 - B cell poor Tocilizumab
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.89
upper limit	0.5

Statistical analysis title	TOC vs. RTX, B cell rich, week 24
Comparison groups	week 24 - B cell rich Rituximab v week 24 - B cell rich Tocilizumab
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.54
upper limit	0.54

Statistical analysis title	TOC vs. RTX, B cell rich, week 48
Comparison groups	week 48 - B cell rich Rituximab v week 48 - B cell rich Tocilizumab
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.58
upper limit	0.62

Other pre-specified: CDAI 50% improvement and CDAI<10.1

End point title	CDAI 50% improvement and CDAI<10.1
End point description:	A patient must have improved by 50% from baseline AND have a low disease activity (CDAI<10.1) to be deemed as a responder
End point type	Other pre-specified
End point timeframe:	
Period 2: Baseline to Week 16	
Period 3: Week 16 to Week 48	

End point values	Rituximab	Tocilizumab	Rituximab	Tocilizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82	79	42	42
Units: Patients				
Responder	17	35	20	30

End point values	ITT week 16 - B cell poor Rituximab	ITT week 16 - B cell poor Tocilizumab	ITT week 16 - B cell rich Rituximab	ITT week 16 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	38	41	33	31
Units: Patients				
Responder	9	19	5	11

End point values	ITT week 16 - B cell poor	ITT week 16 - B cell poor	ITT week 16 - B cell rich	ITT week 16 - B cell rich
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	(RNA_seq) Rituximab	(RNA_seq) Tocilizumab	(RNA_seq) Rituximab	(RNA_seq) Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	32	30	29
Units: Patients				
Responder	4	16	7	9

End point values	PP week 16 - B cell poor Rituximab	PP week 16 - B cell poor Tocilizumab	PP week 16 - B cell rich Rituximab	PP week 16 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	30	31	23
Units: Patients				
Responder	9	17	5	7

End point values	PP week 16 - B cell poor (RNA_seq) Rituximab	PP week 16 - B cell poor (RNA_seq) Tocilizumab	PP week 16 - B cell rich (RNA_seq) Rituximab	PP week 16 - B cell rich (RNA_seq) Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	32	25	28	19
Units: Patients				
Responder	4	15	7	4

End point values	week 24 - B cell poor Rituximab	week 24 - B cell poor Tocilizumab	week 24 - B cell rich Rituximab	week 24 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	21	27	18	20
Units: Patients				
Responder	5	15	5	10

End point values	week 36 - B cell poor Rituximab	week 36 - B cell poor Tocilizumab	week 36 - B cell rich Rituximab	week 36 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	22	17	16
Units: Patients				
Responder	9	12	7	11

End point values	week 48 - B cell poor	week 48 - B cell poor	week 48 - B cell rich	week 48 - B cell rich
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	Rituximab	Tocilizumab	Rituximab	Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17	21	17	16
Units: Patients				
Responder	11	14	6	12

Statistical analyses

Statistical analysis title	TOC vs RTX, B cell poor, ITT
Comparison groups	ITT week 16 - B cell poor Rituximab v ITT week 16 - B cell poor Tocilizumab
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.035
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.227
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.023
upper limit	0.43

Statistical analysis title	TOC vs RTX, B cell rich, ITT
Comparison groups	ITT week 16 - B cell rich Rituximab v ITT week 16 - B cell rich Tocilizumab
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.085
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.203
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.005
upper limit	0.411

Statistical analysis title	TOC vs RTX, B cell poor (RNA-seq), ITT
Comparison groups	ITT week 16 - B cell poor (RNA_seq) Rituximab v ITT week 16 - B cell poor (RNA_seq) Tocilizumab

Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0012
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.379
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.173
upper limit	0.585

Statistical analysis title	TOC vs RTX, B cell rich (RNA-seq), ITT
Comparison groups	ITT week 16 - B cell rich (RNA_seq) Rituximab v ITT week 16 - B cell rich (RNA_seq) Tocilizumab
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.51
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.077
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.149
upper limit	0.303

Statistical analysis title	TOC vs RTX, B cell poor, PP
Comparison groups	PP week 16 - B cell poor Rituximab v PP week 16 - B cell poor Tocilizumab
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0069
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.323
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.099
upper limit	0.548

Statistical analysis title	TOC vs RTX, B cell rich, PP
Comparison groups	PP week 16 - B cell rich Rituximab v PP week 16 - B cell rich Tocilizumab
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.32
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.143
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.085
upper limit	0.371

Statistical analysis title	TOC vs RTX, B cell poor (RNA-seq), PP
Comparison groups	PP week 16 - B cell poor (RNA_seq) Rituximab v PP week 16 - B cell poor (RNA_seq) Tocilizumab
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00022
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.475
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.251
upper limit	0.699

Statistical analysis title	TOC vs RTX, B cell rich (RNA-seq), PP
Comparison groups	PP week 16 - B cell rich (RNA_seq) Rituximab v PP week 16 - B cell rich (RNA_seq) Tocilizumab
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	-0.039
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.283
upper limit	0.204

Other pre-specified: AUC of mean improvement in DAS28 (ESR)

End point title	AUC of mean improvement in DAS28 (ESR)
End point description: Area under the curve (AUC) of mean improvement in DAS28 over time between 0 and 16 weeks and between 0 and 48 weeks	
End point type	Other pre-specified
End point timeframe: Timeframe 2: week 16 Timeframe 3: week 48	

End point values	ITT week 16 - B cell poor Rituximab	ITT week 16 - B cell poor Tocilizumab	ITT week 16 - B cell rich Rituximab	ITT week 16 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	38	41	33	31
Units: area				
number (not applicable)	17.1	31.9	13.9	34.0

End point values	week 48 - B cell poor Rituximab	week 48 - B cell poor Tocilizumab	week 48 - B cell rich Rituximab	week 48 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17	21	17	16
Units: area				
number (not applicable)	83.3	134.0	75.5	132.4

Statistical analyses

Statistical analysis title	TOC vs. RTX, B cell poor, week 16
Comparison groups	ITT week 16 - B cell poor Rituximab v ITT week 16 - B cell poor Tocilizumab
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.01
Method	Mixed models analysis

Statistical analysis title	TOC vs. RTX, B cell rich, week 16
Comparison groups	ITT week 16 - B cell rich Rituximab v ITT week 16 - B cell rich Tocilizumab

Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.01
Method	Mixed models analysis

Statistical analysis title	TOC vs. RTX, B cell poor, week 48
Comparison groups	week 48 - B cell poor Rituximab v week 48 - B cell poor Tocilizumab
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis

Statistical analysis title	TOC vs. RTX, B cell rich, week 48
Comparison groups	week 48 - B cell rich Rituximab v week 48 - B cell rich Tocilizumab
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis

Other pre-specified: AUC of mean improvement in DAS28 (CRP)	
End point title	AUC of mean improvement in DAS28 (CRP)
End point description: Area under the curve (AUC) of mean improvement in DAS28 over time between 0 and 16 weeks and between 0 and 48 weeks	
End point type	Other pre-specified
End point timeframe: Timeframe 2: week 16 Timeframe 3: week 48	

End point values	ITT week 16 - B cell poor Rituximab	ITT week 16 - B cell poor Tocilizumab	ITT week 16 - B cell rich Rituximab	ITT week 16 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	38	41	33	31
Units: area				
number (not applicable)	15.6	23.5	13.1	26.8

End point values	week 48 - B cell poor Rituximab	week 48 - B cell poor Tocilizumab	week 48 - B cell rich Rituximab	week 48 - B cell rich Tocilizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17	21	17	16
Units: area				
number (not applicable)	73.6	107.2	69.0	103.6

Statistical analyses

Statistical analysis title	TOC vs. RTX, B cell poor, week 16
Comparison groups	ITT week 16 - B cell poor Rituximab v ITT week 16 - B cell poor Tocilizumab
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.01
Method	Mixed models analysis

Statistical analysis title	TOC vs. RTX, B cell rich, week 16
Comparison groups	ITT week 16 - B cell rich Tocilizumab v ITT week 16 - B cell rich Rituximab
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.01
Method	Mixed models analysis

Statistical analysis title	TOC vs. RTX, B cell poor, week 48
Comparison groups	week 48 - B cell poor Rituximab v week 48 - B cell poor Tocilizumab
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis

Statistical analysis title	TOC vs. RTX, B cell rich, week 48
Comparison groups	week 48 - B cell rich Rituximab v week 48 - B cell rich Tocilizumab

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis

Other pre-specified: CD20 score

End point title	CD20 score
End point description:	
End point type	Other pre-specified
End point timeframe:	
Timeframe 1: Baseline	
Timeframe 2: week 16	

End point values	Rituximab	Tocilizumab	Rituximab	Tocilizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	24	41	24
Units: score				
arithmetic mean (standard deviation)	1.88 (± 1.4)	1.67 (± 1.3)	0.35 (± 0.8)	1.33 (± 1.3)

Statistical analyses

Statistical analysis title	Week 16 vs. Baseline, Rituximab
Comparison groups	Rituximab v Rituximab
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Week 16 vs. Baseline, Tocilizumab
Comparison groups	Tocilizumab v Tocilizumab
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	TOC vs. RTX, change from baseline
Comparison groups	Tocilizumab v Tocilizumab v Rituximab v Rituximab
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA

Other pre-specified: CD138 score

End point title	CD138 score
End point description:	
End point type	Other pre-specified
End point timeframe:	
Timeframe 1: Baseline	
Timeframe 2: week 16	

End point values	Rituximab	Tocilizumab	Rituximab	Tocilizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	24	41	24
Units: score				
arithmetic mean (standard deviation)	1.68 (± 1.3)	1.58 (± 1.4)	0.35 (± 0.8)	1.33 (± 1.3)

Statistical analyses

Statistical analysis title	Week 16 vs. Baseline, Rituximab
Comparison groups	Rituximab v Rituximab
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Week 16 vs. Baseline, Tocilizumab
Comparison groups	Tocilizumab v Tocilizumab

Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	TOC vs. RTX, change from baseline
Comparison groups	Tocilizumab v Tocilizumab v Rituximab v Rituximab
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Other pre-specified: CD68L score

End point title	CD68L score
End point description:	
End point type	Other pre-specified
End point timeframe:	
Timeframe 1: Baseline	
Timeframe 2: week 16	

End point values	Rituximab	Tocilizumab	Rituximab	Tocilizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	24	41	24
Units: score				
arithmetic mean (standard deviation)	1.2 (± 1)	1.46 (± 1.1)	1.07 (± 0.9)	1.38 (± 1.1)

Statistical analyses

Statistical analysis title	Week 16 vs. Baseline, Rituximab
Comparison groups	Rituximab v Rituximab
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Week 16 vs. Baseline, Tocilizumab
Comparison groups	Tocilizumab v Tocilizumab
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	TOC vs. RTX, change vs. baseline
Comparison groups	Tocilizumab v Tocilizumab v Rituximab v Rituximab
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANCOVA

Other pre-specified: CD68SL score

End point title	CD68SL score
End point description:	
End point type	Other pre-specified
End point timeframe:	
Timeframe 1: Baseline	
Timeframe 2: week 16	

End point values	Rituximab	Tocilizumab	Rituximab	Tocilizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	24	41	24
Units: score				
arithmetic mean (standard deviation)	1.88 (± 0.8)	1.92 (± 1)	1.3 (± 0.6)	0.88 (± 0.7)

Statistical analyses

Statistical analysis title	Week 16 vs. Baseline, Rituximab
Comparison groups	Rituximab v Rituximab

Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Week 16 vs. Baseline, Tocilizumab
Comparison groups	Tocilizumab v Tocilizumab
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	TOC vs. RTX, change from baseline
Comparison groups	Tocilizumab v Tocilizumab v Rituximab v Rituximab
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	ANCOVA

Other pre-specified: CD3 score

End point title	CD3 score
End point description:	
End point type	Other pre-specified
End point timeframe:	
Timeframe 1: Baseline	
Timeframe 2: week 16	

End point values	Rituximab	Tocilizumab	Rituximab	Tocilizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	24	41	24
Units: score				
arithmetic mean (standard deviation)	1.63 (± 1.1)	1.58 (± 1.1)	1.52 (± 1.2)	1.42 (± 1.2)

Statistical analyses

Statistical analysis title	Week 16 vs. baseline, Rituximab
Comparison groups	Rituximab v Rituximab
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Week 16 vs. baseline, Tocilizumab
Comparison groups	Tocilizumab v Tocilizumab
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	TOC vs. RTX, change from baseline
Comparison groups	Tocilizumab v Tocilizumab v Rituximab v Rituximab
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANCOVA

Other pre-specified: CD79a score

End point title	CD79a score
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End point description:

End point type	Other pre-specified
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End point timeframe:

Timeframe 1: Baseline

Timeframe 2: week 16

End point values	Rituximab	Tocilizumab	Rituximab	Tocilizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	24	41	24
Units: score				
arithmetic mean (standard deviation)	1.77 (± 1.4)	1.54 (± 1.3)	0.9 (± 1.1)	1.47 (± 1.2)

Statistical analyses

Statistical analysis title	Week 16 vs. baseline, Rituximab
Comparison groups	Rituximab v Rituximab
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Week 16 vs. baseline, Tocilizumab
Comparison groups	Tocilizumab v Tocilizumab
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	TOC vs. RTX, change from baseline
Comparison groups	Tocilizumab v Tocilizumab v Rituximab v Rituximab
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA

Other pre-specified: Synovial score

End point title	Synovial score
End point description:	
End point type	Other pre-specified
End point timeframe:	
Timeframe 1: Baseline	
Timeframe 2: week 16	

End point values	Rituximab	Tocilizumab	Rituximab	Tocilizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	24	41	24
Units: score				
arithmetic mean (standard deviation)	4.63 ($\pm$ 2.5)	4.38 ($\pm$ 2.8)	3.23 ($\pm$ 2)	3.46 ($\pm$ 2.4)

Statistical analyses

Statistical analysis title	Week 16 vs. baseline, Rituximab
Comparison groups	Rituximab v Rituximab
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Week 16 vs. baseline, Tocilizumab
Comparison groups	Tocilizumab v Tocilizumab
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	TOC vs. RTX, change from baseline
Comparison groups	Tocilizumab v Tocilizumab v Rituximab v Rituximab
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANCOVA

Other pre-specified: CD21 status

End point title	CD21 status
End point description:	
End point type	Other pre-specified
End point timeframe:	
Timeframe 1: Baseline	
Timeframe 2: week 16	

End point values	Rituximab	Tocilizumab	Rituximab	Tocilizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	24	41	24
Units: Patients	35	21	39	20

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were recorded from the time of the first trial specific assessment/procedure was undertaken (at the screening visit) until LPLV (+30 days where patients only participated up until week 48 (i.e. the end of the trial treatment period)).

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Rituximab
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Reporting group description:

Patients on rituximab at the time of the event

Reporting group title	Tocilizumab
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Reporting group description:

Patients on tocilizumab at the time of the event

Serious adverse events	Rituximab	Tocilizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 108 (7.41%)	18 / 117 (15.38%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Drainage of cyst around dental implant, removal implant			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Drainage of Pilonidal Abscess			
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hospitalisation following (L) 4th toe amputation and (R) 3rd toe PIP fusion			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Total Knee Replacement subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain requiring hospital admission			
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Cytokine Release Syndrome			
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Rt side Pleural effusion			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of COPD			
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicide			

subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
RE-admission to hospital, post MI. Repeat coronary angiogram			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Persistent Chest Pain, Mild Left Ventricular impairment			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain during cardiac rehabilitation			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden onset chest pain			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Seizure, Fracture of the Humerous/Femur			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Corneal melt			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea - salmonella			

subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Abdominal pain (urinoma)			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
urinary tract infection			
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Parathyroid adenoma requiring intervention			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pain in left leg (scan showed no blood clot)			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hospitalisation for elective surgery to left Hallux vagus (osteotomy)			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pilonidal sinus caused by an infectious agent			

subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Rituximab	Tocilizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	57 / 108 (52.78%)	72 / 117 (61.54%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Synovial cyst			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Vascular disorders			
Angina			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Bleeding			
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences (all)	1	0	
Blood pressure high			
subjects affected / exposed	0 / 108 (0.00%)	2 / 117 (1.71%)	
occurrences (all)	0	2	
Bruising of foot			
subjects affected / exposed	1 / 108 (0.93%)	1 / 117 (0.85%)	
occurrences (all)	1	1	
Capillary disorder			
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	0 / 108 (0.00%)	2 / 117 (1.71%)	
occurrences (all)	0	2	
Dizziness postural			
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences (all)	1	0	
Dot hemorrhages			

subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Epistaxis		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Felt faint		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Foot ulcer		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	2
Hematoma infection		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Hypertension		
subjects affected / exposed	3 / 108 (2.78%)	1 / 117 (0.85%)
occurrences (all)	4	1
Light headedness		
subjects affected / exposed	2 / 108 (1.85%)	1 / 117 (0.85%)
occurrences (all)	2	1
Nose bleed		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Purpura		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
PV bleeding		
subjects affected / exposed	2 / 108 (1.85%)	1 / 117 (0.85%)
occurrences (all)	2	1
Rectal bleeding		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Skin sores		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Spotting vaginal		

subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences (all)	1	0	
Vasculitis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Artificial crown procedure			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Cataract operation			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Coronary arterial stent insertion			
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences (all)	1	0	
Cyst removal			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Drainage of abscess			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Foot surgery			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Hernia repair			
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences (all)	1	0	
Knee total replacement			
subjects affected / exposed	2 / 108 (1.85%)	0 / 117 (0.00%)	
occurrences (all)	2	0	
Osteotomy			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Removal of foreign body			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	

Tooth extraction subjects affected / exposed occurrences (all)	0 / 108 (0.00%) 0	1 / 117 (0.85%) 2	
Tooth repair subjects affected / exposed occurrences (all)	0 / 108 (0.00%) 0	1 / 117 (0.85%) 1	
General disorders and administration site conditions			
Adverse drug reaction subjects affected / exposed occurrences (all)	3 / 108 (2.78%) 4	0 / 117 (0.00%) 0	
Ankle oedema subjects affected / exposed occurrences (all)	0 / 108 (0.00%) 0	1 / 117 (0.85%) 1	
Asthenia subjects affected / exposed occurrences (all)	0 / 108 (0.00%) 0	1 / 117 (0.85%) 1	
Axillary pain subjects affected / exposed occurrences (all)	0 / 108 (0.00%) 0	1 / 117 (0.85%) 1	
Chest pain subjects affected / exposed occurrences (all)	0 / 108 (0.00%) 0	2 / 117 (1.71%) 2	
Edema of lower extremities subjects affected / exposed occurrences (all)	1 / 108 (0.93%) 1	0 / 117 (0.00%) 0	
Extravasation of drug subjects affected / exposed occurrences (all)	0 / 108 (0.00%) 0	1 / 117 (0.85%) 1	
Fatigue subjects affected / exposed occurrences (all)	2 / 108 (1.85%) 2	3 / 117 (2.56%) 5	
Fever subjects affected / exposed occurrences (all)	0 / 108 (0.00%) 0	1 / 117 (0.85%) 1	
Flank pain			

subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Flu like symptoms		
subjects affected / exposed	5 / 108 (4.63%)	2 / 117 (1.71%)
occurrences (all)	5	2
General symptoms		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Generalised aching		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Lethargy		
subjects affected / exposed	0 / 108 (0.00%)	2 / 117 (1.71%)
occurrences (all)	0	2
Localised superficial swelling, mass or lump		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Oedema of lower extremities		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Pain		
subjects affected / exposed	3 / 108 (2.78%)	0 / 117 (0.00%)
occurrences (all)	3	0
Peripheral edema		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Pitting oedema		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Suprapubic pain		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Swelling of feet		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1

Swelling of fingers subjects affected / exposed occurrences (all)	0 / 108 (0.00%) 0	1 / 117 (0.85%) 1	
Swelling of legs subjects affected / exposed occurrences (all)	0 / 108 (0.00%) 0	1 / 117 (0.85%) 1	
Thoracalgia subjects affected / exposed occurrences (all)	1 / 108 (0.93%) 1	0 / 117 (0.00%) 0	
Immune system disorders			
Allergic reaction subjects affected / exposed occurrences (all)	1 / 108 (0.93%) 1	0 / 117 (0.00%) 0	
Allergic skin reaction subjects affected / exposed occurrences (all)	1 / 108 (0.93%) 1	1 / 117 (0.85%) 1	
Angioedema subjects affected / exposed occurrences (all)	1 / 108 (0.93%) 1	0 / 117 (0.00%) 0	
Asthmatic attack subjects affected / exposed occurrences (all)	1 / 108 (0.93%) 1	0 / 117 (0.00%) 0	
Exacerbation of asthma subjects affected / exposed occurrences (all)	1 / 108 (0.93%) 1	0 / 117 (0.00%) 0	
Hay fever subjects affected / exposed occurrences (all)	0 / 108 (0.00%) 0	1 / 117 (0.85%) 1	
Infusion related reaction subjects affected / exposed occurrences (all)	1 / 108 (0.93%) 1	1 / 117 (0.85%) 1	
Rheumatoid arthritis flare up subjects affected / exposed occurrences (all)	1 / 108 (0.93%) 1	2 / 117 (1.71%) 2	
Seasonal allergy			

subjects affected / exposed occurrences (all)	1 / 108 (0.93%) 1	0 / 117 (0.00%) 0	
Reproductive system and breast disorders			
Genital ulceration subjects affected / exposed occurrences (all)	1 / 108 (0.93%) 1	0 / 117 (0.00%) 0	
Metorrhagia subjects affected / exposed occurrences (all)	0 / 108 (0.00%) 0	1 / 117 (0.85%) 1	
Vaginal discharge subjects affected / exposed occurrences (all)	1 / 108 (0.93%) 1	1 / 117 (0.85%) 2	
Vaginal prolapse subjects affected / exposed occurrences (all)	1 / 108 (0.93%) 1	0 / 117 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders			
Acute nasal congestion subjects affected / exposed occurrences (all)	1 / 108 (0.93%) 1	0 / 117 (0.00%) 0	
Breathlessness subjects affected / exposed occurrences (all)	0 / 108 (0.00%) 0	2 / 117 (1.71%) 2	
Chest infection subjects affected / exposed occurrences (all)	8 / 108 (7.41%) 11	12 / 117 (10.26%) 14	
Cold subjects affected / exposed occurrences (all)	5 / 108 (4.63%) 5	6 / 117 (5.13%) 6	
Common cold subjects affected / exposed occurrences (all)	7 / 108 (6.48%) 7	4 / 117 (3.42%) 5	
COPD exacerbation subjects affected / exposed occurrences (all)	0 / 108 (0.00%) 0	2 / 117 (1.71%) 2	
Cough			

subjects affected / exposed	6 / 108 (5.56%)	2 / 117 (1.71%)
occurrences (all)	6	2
Dry cough		
subjects affected / exposed	3 / 108 (2.78%)	2 / 117 (1.71%)
occurrences (all)	3	2
Dyspnoea		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Lower respiratory tract infection		
subjects affected / exposed	3 / 108 (2.78%)	2 / 117 (1.71%)
occurrences (all)	3	2
Nasal mucosal blistering		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Nasal ulcer		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Pleurisy		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Pneumonia		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Productive cough		
subjects affected / exposed	1 / 108 (0.93%)	1 / 117 (0.85%)
occurrences (all)	1	1
Respiratory tract infection		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Rhinorrhoea		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Runny nose		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Shortness of breath		

subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	5 / 108 (4.63%)	5 / 117 (4.27%)	
occurrences (all)	5	5	
Psychiatric disorders			
Alzheimer's disease			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Depressed state			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Depression			
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences (all)	1	0	
Sleeplessness			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Stress			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Investigations			
Abnormal LFTs			
subjects affected / exposed	0 / 108 (0.00%)	4 / 117 (3.42%)	
occurrences (all)	0	4	
ALT increased			
subjects affected / exposed	1 / 108 (0.93%)	8 / 117 (6.84%)	
occurrences (all)	1	11	
Anti-transglutaminase antibody increased			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
AST increased			

subjects affected / exposed	0 / 108 (0.00%)	2 / 117 (1.71%)
occurrences (all)	0	3
Bilirubin increased		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Biopsy of lymph node		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Blood pressure increased		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Cerebellum MRI signal changes		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Cervical smear test abnormal		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Colonoscopy		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Creatinine abnormal NOS		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Creatinine high		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Cyst aspiration		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
ECG normal		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Haemoglobin low		
subjects affected / exposed	2 / 108 (1.85%)	0 / 117 (0.00%)
occurrences (all)	2	0
Heart rate increased		

subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences (all)	1	0	
Hemoglobin low			
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences (all)	1	0	
Knee arthroscopy			
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences (all)	1	0	
Low density lipoprotein cholesterol high			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Low platelets			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	2	
Mean corpuscular volume increased			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Potassium low			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Thyroid stimulating hormone			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Transaminases increased			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Vitamin D low			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Weight loss			
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			

Accidental overdose (therapeutic agent)		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Bee sting		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Biceps tendon rupture		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Bite		
subjects affected / exposed	2 / 108 (1.85%)	1 / 117 (0.85%)
occurrences (all)	2	1
Bruising		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Cut wound		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Fall		
subjects affected / exposed	2 / 108 (1.85%)	5 / 117 (4.27%)
occurrences (all)	3	5
Infusion related reaction		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Open wound of tooth (broken), uncomplicated		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Pain post biopsy		
subjects affected / exposed	1 / 108 (0.93%)	1 / 117 (0.85%)
occurrences (all)	1	1
Scratch eye		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Tronchanteric bursitis		

subjects affected / exposed occurrences (all)	1 / 108 (0.93%) 1	0 / 117 (0.00%) 0	
Wasp sting subjects affected / exposed occurrences (all)	0 / 108 (0.00%) 0	1 / 117 (0.85%) 1	
Wound subjects affected / exposed occurrences (all)	0 / 108 (0.00%) 0	1 / 117 (0.85%) 1	
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	1 / 108 (0.93%) 1	0 / 117 (0.00%) 0	
Nervous system disorders Demyelination subjects affected / exposed occurrences (all)	0 / 108 (0.00%) 0	1 / 117 (0.85%) 1	
Facial neuralgia subjects affected / exposed occurrences (all)	0 / 108 (0.00%) 0	1 / 117 (0.85%) 1	
Headache subjects affected / exposed occurrences (all)	9 / 108 (8.33%) 11	4 / 117 (3.42%) 5	
Headache recurrent subjects affected / exposed occurrences (all)	1 / 108 (0.93%) 1	0 / 117 (0.00%) 0	
Migraine with aura subjects affected / exposed occurrences (all)	0 / 108 (0.00%) 0	1 / 117 (0.85%) 1	
Neurological impairment subjects affected / exposed occurrences (all)	1 / 108 (0.93%) 1	0 / 117 (0.00%) 0	
Pain head subjects affected / exposed occurrences (all)	0 / 108 (0.00%) 0	1 / 117 (0.85%) 1	
Sensory loss			

subjects affected / exposed occurrences (all)	1 / 108 (0.93%) 1	0 / 117 (0.00%) 0	
Tinnitus subjects affected / exposed occurrences (all)	0 / 108 (0.00%) 0	1 / 117 (0.85%) 1	
Trembling subjects affected / exposed occurrences (all)	0 / 108 (0.00%) 0	1 / 117 (0.85%) 1	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	1 / 108 (0.93%) 1	1 / 117 (0.85%) 1	
Leucopenia subjects affected / exposed occurrences (all)	1 / 108 (0.93%) 1	2 / 117 (1.71%) 2	
Lymphangitis subjects affected / exposed occurrences (all)	0 / 108 (0.00%) 0	1 / 117 (0.85%) 1	
Neutropenia subjects affected / exposed occurrences (all)	0 / 108 (0.00%) 0	3 / 117 (2.56%) 4	
Normocytic anaemia subjects affected / exposed occurrences (all)	0 / 108 (0.00%) 0	1 / 117 (0.85%) 1	
Swollen glands subjects affected / exposed occurrences (all)	0 / 108 (0.00%) 0	1 / 117 (0.85%) 1	
Ear and labyrinth disorders			
Ear congestion subjects affected / exposed occurrences (all)	0 / 108 (0.00%) 0	1 / 117 (0.85%) 1	
Ear disorder NOS subjects affected / exposed occurrences (all)	0 / 108 (0.00%) 0	1 / 117 (0.85%) 1	
Otalgia			

subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences (all)	1	0	
Vertigo			
subjects affected / exposed	1 / 108 (0.93%)	1 / 117 (0.85%)	
occurrences (all)	1	1	
Eye disorders			
Bilateral cataracts			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Blepharitis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Blurred vision			
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis			
subjects affected / exposed	0 / 108 (0.00%)	2 / 117 (1.71%)	
occurrences (all)	0	3	
Dry eyes			
subjects affected / exposed	2 / 108 (1.85%)	0 / 117 (0.00%)	
occurrences (all)	3	0	
Lesion corneal			
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences (all)	1	0	
Ocular pain			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Subconjunctival hemorrhage			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Xerophthalmia			
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal bloating			

subjects affected / exposed	1 / 108 (0.93%)	1 / 117 (0.85%)
occurrences (all)	1	1
Abdominal pain		
subjects affected / exposed	1 / 108 (0.93%)	2 / 117 (1.71%)
occurrences (all)	1	2
Abdominal pain lower		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Abdominal tenderness		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Acid reflux (esophageal)		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Alternation between constipation and diarrhoea		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Bloody diarrhoea		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Colonic tubular adenoma		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Constipation		
subjects affected / exposed	2 / 108 (1.85%)	0 / 117 (0.00%)
occurrences (all)	2	0
Diarrhoea		
subjects affected / exposed	4 / 108 (3.70%)	2 / 117 (1.71%)
occurrences (all)	4	2
Dyspepsia		
subjects affected / exposed	1 / 108 (0.93%)	3 / 117 (2.56%)
occurrences (all)	1	3
Dysphagia		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0

Emesis		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Epigastralgia		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Epigastric discomfort		
subjects affected / exposed	1 / 108 (0.93%)	1 / 117 (0.85%)
occurrences (all)	1	1
Food poisoning		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Indigestion		
subjects affected / exposed	1 / 108 (0.93%)	1 / 117 (0.85%)
occurrences (all)	1	1
Itchy throat		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Lip ulcer		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Loose stools		
subjects affected / exposed	2 / 108 (1.85%)	0 / 117 (0.00%)
occurrences (all)	2	0
Mouth ulcer		
subjects affected / exposed	2 / 108 (1.85%)	7 / 117 (5.98%)
occurrences (all)	2	8
Nausea		
subjects affected / exposed	3 / 108 (2.78%)	2 / 117 (1.71%)
occurrences (all)	3	2
Nausea vomiting and diarrhoea		
subjects affected / exposed	1 / 108 (0.93%)	1 / 117 (0.85%)
occurrences (all)	2	1
Oral mucosa bleeding		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1

Sensitive mouth			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Sickness/nausea			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Sore mouth			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Sore throat			
subjects affected / exposed	2 / 108 (1.85%)	3 / 117 (2.56%)	
occurrences (all)	2	3	
Stomatitis			
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences (all)	1	0	
Throat pain			
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences (all)	1	0	
Tongue ulceration			
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences (all)	1	0	
Ulcer aphthous oral			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Upset stomach			
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	4 / 108 (3.70%)	1 / 117 (0.85%)	
occurrences (all)	7	1	
Watery Diarrhoea			
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Biliary microlithiasis			

subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences (all)	1	0	
Dilatation biliary tract			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Hypertransaminasemia			
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Butterfly rash			
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences (all)	1	0	
Cutaneous vasculitis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Dry scalp			
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences (all)	1	0	
Dysaesthesia			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	2	
Erythema			
subjects affected / exposed	2 / 108 (1.85%)	0 / 117 (0.00%)	
occurrences (all)	2	0	
Erythema facial			
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences (all)	1	0	
Extensive rash of forearm			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Folliculitis			
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences (all)	1	0	
Generalised itching			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	

Hair loss		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Hidradenitis		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Infected skin ulcer		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Irritation skin		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Itching		
subjects affected / exposed	2 / 108 (1.85%)	0 / 117 (0.00%)
occurrences (all)	2	0
Itchy rash		
subjects affected / exposed	4 / 108 (3.70%)	0 / 117 (0.00%)
occurrences (all)	4	0
Itchy scalp		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Macular rash		
subjects affected / exposed	2 / 108 (1.85%)	0 / 117 (0.00%)
occurrences (all)	2	0
Nail discomfort		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Nail infection		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Papular rash		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Paronychia		
subjects affected / exposed	1 / 108 (0.93%)	1 / 117 (0.85%)
occurrences (all)	1	1

Pins and needles		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Prickly heat		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Pruritic rash		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Pruritus		
subjects affected / exposed	1 / 108 (0.93%)	1 / 117 (0.85%)
occurrences (all)	1	1
Rash		
subjects affected / exposed	1 / 108 (0.93%)	6 / 117 (5.13%)
occurrences (all)	1	6
Rash on face		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Redness of face		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Scalp rash		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Skin infection		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Skin lesion		
subjects affected / exposed	1 / 108 (0.93%)	2 / 117 (1.71%)
occurrences (all)	1	2
Skin rash		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Tingling sensation		
subjects affected / exposed	1 / 108 (0.93%)	1 / 117 (0.85%)
occurrences (all)	2	2

Urticarial subjects affected / exposed occurrences (all)	1 / 108 (0.93%) 1	0 / 117 (0.00%) 0	
Urticarial rash subjects affected / exposed occurrences (all)	0 / 108 (0.00%) 0	1 / 117 (0.85%) 1	
Vasculitic rash subjects affected / exposed occurrences (all)	0 / 108 (0.00%) 0	1 / 117 (0.85%) 1	
Skin lesion NOS subjects affected / exposed occurrences (all)	0 / 108 (0.00%) 0	1 / 117 (0.85%) 1	
Renal and urinary disorders			
Cystitis subjects affected / exposed occurrences (all)	0 / 108 (0.00%) 0	1 / 117 (0.85%) 1	
Pelvic pain subjects affected / exposed occurrences (all)	0 / 108 (0.00%) 0	1 / 117 (0.85%) 1	
Urinary frequency subjects affected / exposed occurrences (all)	2 / 108 (1.85%) 2	0 / 117 (0.00%) 0	
Urinary infection subjects affected / exposed occurrences (all)	2 / 108 (1.85%) 3	5 / 117 (4.27%) 5	
Urinary retention subjects affected / exposed occurrences (all)	0 / 108 (0.00%) 0	1 / 117 (0.85%) 1	
Urinary tract infection subjects affected / exposed occurrences (all)	3 / 108 (2.78%) 4	9 / 117 (7.69%) 11	
UTI subjects affected / exposed occurrences (all)	1 / 108 (0.93%) 1	1 / 117 (0.85%) 3	
Musculoskeletal and connective tissue disorders			

Achilles tendon pain		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Arthralgia aggravated		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Avascular necrosis		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Back pain		
subjects affected / exposed	3 / 108 (2.78%)	3 / 117 (2.56%)
occurrences (all)	3	3
Calf pain		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Fascitis plantar		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Finger cramps		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Frozen shoulder		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Joint clicking		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Joint infection		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Knee effusion		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Knee ligament injury		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1

Knee pain		
subjects affected / exposed	2 / 108 (1.85%)	1 / 117 (0.85%)
occurrences (all)	2	1
Leg pain		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Low back pain		
subjects affected / exposed	4 / 108 (3.70%)	1 / 117 (0.85%)
occurrences (all)	4	1
Muscle twitch		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Myalgia		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Neck pain		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Neck pain (with radiation)		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Osteoarthritis of cervical spine		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Pain in (l) knee		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Pain in (l) shoulder		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Pain in (r) elbow		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Pain in arm		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	2	0

Pain in hip			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Pain in lumbar spine			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Pain in toe			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Restless legs syndrome			
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences (all)	1	0	
Shoulder pain			
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences (all)	1	0	
Swollen wrists			
subjects affected / exposed	1 / 108 (0.93%)	1 / 117 (0.85%)	
occurrences (all)	1	1	
Wrist pain			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Infections and infestations			
Abscess on buttock			
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences (all)	1	0	
Acute bronchitis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Acute infective bronchitis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Acute sinusitis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Acute tracheobronchitis			

subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Asymptomatic bacteriuria		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Breast abscess		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Bronchitis		
subjects affected / exposed	2 / 108 (1.85%)	3 / 117 (2.56%)
occurrences (all)	2	4
Cellulitis		
subjects affected / exposed	0 / 108 (0.00%)	2 / 117 (1.71%)
occurrences (all)	0	2
Cellulitis of legs		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Cold sores		
subjects affected / exposed	1 / 108 (0.93%)	4 / 117 (3.42%)
occurrences (all)	1	4
Cold sores lip		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Cold sores mouth		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Coryza		
subjects affected / exposed	4 / 108 (3.70%)	0 / 117 (0.00%)
occurrences (all)	4	0
Dental abscess		
subjects affected / exposed	2 / 108 (1.85%)	0 / 117 (0.00%)
occurrences (all)	2	0
Ear infection		
subjects affected / exposed	1 / 108 (0.93%)	1 / 117 (0.85%)
occurrences (all)	1	1
Epididymitis		

subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Eye infection		
subjects affected / exposed	1 / 108 (0.93%)	1 / 117 (0.85%)
occurrences (all)	2	1
Fever blister		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Flu		
subjects affected / exposed	4 / 108 (3.70%)	1 / 117 (0.85%)
occurrences (all)	4	1
Foot infection		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Fungal skin infection		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Gastroenteritis		
subjects affected / exposed	1 / 108 (0.93%)	3 / 117 (2.56%)
occurrences (all)	1	3
Gingivitis		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Haemophilus influenza infection		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Hand-foot-and-mouth disease		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Herpes simplex		
subjects affected / exposed	1 / 108 (0.93%)	1 / 117 (0.85%)
occurrences (all)	1	1
Infected corn		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Infected insect bite		

subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Infected toe		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Influenza		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Laryngitis		
subjects affected / exposed	0 / 108 (0.00%)	2 / 117 (1.71%)
occurrences (all)	0	3
Mastitis		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Mycosis		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Oral thrush		
subjects affected / exposed	1 / 108 (0.93%)	1 / 117 (0.85%)
occurrences (all)	1	1
Otitis		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Perineal abscess		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	2
Periorbital cellulitis		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Pharyngitis		
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)
occurrences (all)	1	0
Respiratory infection		
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	1
Shingles		

subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences (all)	1	0	
Sinus infection			
subjects affected / exposed	1 / 108 (0.93%)	1 / 117 (0.85%)	
occurrences (all)	1	1	
Sinusitis			
subjects affected / exposed	0 / 108 (0.00%)	2 / 117 (1.71%)	
occurrences (all)	0	2	
Streptococcal pharyngitis			
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences (all)	1	0	
Thrush vaginal			
subjects affected / exposed	1 / 108 (0.93%)	2 / 117 (1.71%)	
occurrences (all)	1	2	
Tooth abscess			
subjects affected / exposed	0 / 108 (0.00%)	3 / 117 (2.56%)	
occurrences (all)	0	3	
Tooth infection			
subjects affected / exposed	1 / 108 (0.93%)	1 / 117 (0.85%)	
occurrences (all)	1	1	
Vaginal candidiasis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Vaginal mycosis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Wound infection			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 108 (0.93%)	0 / 117 (0.00%)	
occurrences (all)	1	0	
Hyperlipidaemia			
subjects affected / exposed	0 / 108 (0.00%)	1 / 117 (0.85%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 May 2013	Update to Protocol: Change to biopsy schedule and primary end point (24 weeks to 16 weeks) Revision (reduction) of study blood assessments Addition of use of PICs Clarification of fourth unknown stratum for randomisation procedures Clarification of SAE reporting period Clarification of procedures for early withdrawal Clarification of events not to be reported as SAEs Clarification of treatment period and observation period Clarification of permitted steroid use Collection of new data fields; previous anti-TNF and total Chol, HDL, LDL, tryglycerides. Updates to PIS: Less prescriptive information on trial hypothesis to reduce patient bias Clarification of potential to switch medication from Weeks 16 to 48 Clarification of treatment period and observation period and visit schedules Clarification for treatment after trial has ended. Inclusion of emergency contact details. Other formatting changes, clarifications, corrections to the above documents.
03 September 2013	Addition of trial sites Change of PI (Barts Health)
02 May 2014	1. Expansion of synovial biopsy technique to allow use of arthroscopic biopsy as well as US guided needle synovial biopsy 2. Additional exclusion criteria (#4- Prior exposure to Rituximab or Tocilizumab for the treatment of RA) 3. Amendment to exclusion criteria already listed to include latex allergy or allergy to any excipients of Rituximab and Tocilizumab 4. Clarifications to procedures for administration of IMPs (specifically Rituximab) 5. Relaxation of requirements/restrictions for corticosteroid use during treatment 6. Amendment to requirements for routine bloods at screening and biopsy time points 7. Clarifications on treatment schedule for both IMPs 8. Amendment to requirement for x-ray of hands and feet at Baseline visit 9. Addition of instructions to conduct tender joint (TJC) and swollen joint count (SJC). 10. Extra study specific blood time point at week 28 and clarification of potential for change to study blood schedule (in line with any potential switch in trial treatment as per protocol). 11. Additional PAXgene RNA tube at Biopsy visit, Week 16, Week 48 and Week 96 time-points. 12. Amendment to criteria for Early Withdrawal and clarification that this refers specifically to treatment cessation 13. Clarification on procedures for data collection and follow up for Withdrawn Subjects 14. Clarification of procedures for SAE reporting post cessation of treatment 15. Additional secondary endpoints 16. Clarification of no safety endpoints 17. APPLICABLE only to lead site (Mile End Hospital, Barts Health): Revision of optional biopsy time point so that, for any patient, who chooses to have any subsequent biopsy [beyond week 16 visit], a biopsy may be taken at such time that a patient switches treatment (ie deemed a non-responder).
21 October 2014	Addition of trial sites (Southampton and Basildon)

26 November 2014	Addition of trial sites (Southend and Aintree/Liverpool)
09 January 2015	1. Addition of optional biopsy consent form 2. Protocol: Addition of faster infusion schedule for second and subsequent Rituximab infusion, as per Rituximab SmPC. 3. Protocol: Addition of a time point (within 4 weeks prior to Visit 3 Baseline) where restrictions apply for the use of corticosteroids. 4. Protocol: Hepatitis B screening has been made mandatory to be consistent with SmPC for Rituximab (updated on 23/05/2014). Exclusion criteria #11 amended to "Known HIV or hepatitis B/C infection. Hepatitis B screening test must be performed at or in the preceding 3 months of screening visit." 5. Protocol: Clarification on reporting of laboratory abnormalities to define how they should be reported as AE, SAE or SUSAR. 6. Protocol: Clarification on exclusion criteria #24. New wording: "24. Patients currently recruited to other clinical trial(s) involving an investigational medicinal product (except any observational follow-up periods not involving an IMP)." 7. Patient Information Sheet: description of indemnity was amended 8. Patient Information Sheet: Explanation on follow up after withdrawal was made clearer 9. Protocol: US time-pointss have been amended (a total of 10 time-points remains unchanged) (taken at baseline, not week 8- visit 5) 10. SmPC: Update on SmPCs for Rituximab and Tocilizumab 11. Addition of Pre and Post Biopsy Assessment Form Other minor formatting changes, clarifications, corrections to the above documents.
17 June 2015	1. Addition of trial sites (Manchester, Bath, and Guys). 2. Change of PI at Homerton trial site (Change from Beena Hamed to Piero Reynolds)
18 August 2015	Addition of trial site (Leeds).
15 August 2016	1. Change of Sponsor Representative. 2. Change of follow-up period for some patients resulting in updates to the end of study definition, PIS and ICF. 3. Update to sample size calculation. 4. New document 'end of trial letter' for participants. 5. Clarifications to existing inclusion and exclusion criteria. 6. Clarification that RF/CCP tests should be conducted at screening unless the tests have been done previously and do not need repeating as per local guidelines. 7. Clarification that baseline assessments should be done within a +/- 7 day window 8. Clarification that X-rays must be performed as per routine screening for tuberculosis at screening 9. Removal of text regarding statins as patients will be managed as per routine care 10. Clarification the serum immunoglobulins must be performed at screening (unless done 8 weeks before) 11. Clarification that a patient deemed a non-responder at visit 7 (week 16) can switch treatment at their subsequent visit 12. Clarification that for visits 7 onwards a patient can switch treatment at the following visit 13. Addition of secondary endpoints 14. Other minor amendments to protocol
30 August 2017	Addition of poster for recruitment purposes Extension of recruitment period to 1st December 2017 Minor change to patient end of trial letter in line with recruitment extension Use of patient video (already approved for STRAP trial) for purposes of R4RA trial recruitment.

18 December 2017	1. Clarification on end of trial- The R4-RA trial has undergone 3 no-cost extensions therefore the trial must cease recruitment in December 2017 or when at least 86 B-cell poor and at least 51-B-cell rich patients (numbers required for 90% power) has been reached, whichever comes first. 2. Digital Image analysis added to protocol 3. Change of end of trial definition from LPLV to 6 months after the LPLV to allow time for sample processing and image analysis, if required. 4. Amendments and clarifications to study endpoints
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study has some limitations including, uncertainty about the optimal B-cell poor/rich classification (cellular v molecular), the inclusion of an active comparator (tocilizumab) that, similarly to rituximab, modulates B cell function and survival.
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Notes: