Electronic supplementary information

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Long-term efficacy and safety of biosimilar CT-P10 versus innovator rituximab in rheumatoid arthritis: 48-week results from a randomized Phase 3 trial

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Table S1 Mean scores and change from baseline in ACR individual components (efficacy population [a])

	CT-P10 (n=155)		US-RTX (n=144)		EU-RTX (n=59)		Combined RTX[b] (n=203)	
	Actual result	**Change from baseline**	**Actual result**	**Change from baseline**	**Actual result**	**Change from baseline**	**Actual result**	**Change from baseline**
Number of tender joints								
Baseline	22.2		21.2		22.1		21.5	
Week 24	7.2	–14.7	6.8	–14.3	8.8	–13.3	7.4	–14.0
Week 48	5.9	–16.5	5.2	–15.8	6.9	–14.3	5.7	–15.4
Number of swollen joints								
Baseline	15.1		13.9		15.2		14.3	
Week 24	3.3	–11.5	3.5	–10.4	5.6	–9.6	4.1	–10.1
Week 48	2.5	–12.6	2.5	–11.3	4.0	–10.3	3.0	–11.0
Patient's assessment of pain using VAS								
Baseline	70.4		69.3		72.7		70.3	
Week 24	32.8	–36.7	31.9	–37.1	34.3	–38.4	32.6	–37.5
Week 48	29.6	–39.7	32.1	–36.6	28.7	–43.8	31.1	–38.8
Patient's global assessment of disease activity using VAS								
Baseline	68.9		68.6		71.8		69.5	
Week 24	33.4	–35.1	32.2	–35.9	34.4	–37.3	32.9	–36.4
Week 48	29.7	–38.4	31.6	–36.6	28.9	–42.6	30.8	–38.4
Physician's global assessment of disease activity using VAS								

Baseline	65.2		64.4		66.1		64.9	
Week 24	25.4	–39.3	23.4	–41.1	39.7	–36.1	25.3	–39.6
Week 48	20.3	–44.4	21.1	–43.5	22.9	–43.0	21.6	–43.3
HAQ estimate of physical ability								
Baseline	1.73		1.67		1.69		1.67	
Week 24	1.04	–0.65	1.11	–0.54	1.11	–0.57	1.11	–0.55
Week 48	0.98	–0.70	1.04	–0.59	0.96	–0.71	1.02	–0.63
CRP, mg/dL								
Baseline	2.2		2.3		3.4		2.6	
Week 24	1.0	–1.2	1.0	–1.2	1.3	–2.2	1.1	–1.5
Week 48	0.6	–1.5	1.1	–1.2	0.9	–2.4	1.0	–1.5
ESR, mm/h								
Baseline	55.1		56.4		59		203	
Week 24	32.4	–23.8	33.2	–23.4	32.7	–18.8	33.0	–22.0
Week 48	29.0	–27.0	32.8	–24.4	25.8	–25.6	30.8	–24.7

ACR American College of Rheumatology, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *EU* European Union, *HAQ* Health Assessment Questionnaire, *RTX* rituximab, *US* United States, *VAS* visual analogue scale

[a]Week 48 data are from the efficacy population–2nd treatment course subset (CT-P10, n=139; US-RTX, n=135; EU-RTX, n=53; Combined RTX, n=193). [b]US-RTX and EU-RTX groups combined.

Table S2 Change from baseline in DAS28 by FcγR subtypes (efficacy population[a])

	CT-P10 (n=155)		US-RTX (n=144)		EU-RTX (n=59)		Combined RTX[b] (n=203)	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
DAS28-ESR								
Week 24								
FcγRIIa subtype								
RR	23	–2.6 (1.2)	15	–1.9 (1.0)	9	–2.6 (0.9)	24	–2.2 (1.0)
HR+HH	99	–2.6 (1.1)	108	–2.7 (1.1)	40	–2.3 (1.3)	148	–2.6 (1.2)
FcγRIIIa subtype								
FF	66	–2.6 (1.1)	53	–2.6 (1.3)	23	–2.6 (1.3)	76	–2.6 (1.3)
FV+VV	50	–2.6 (1.2)	69	–2.6 (1.0)	25	–2.0 (1.4)	94	–2.4 (1.1)
Week 48								
FcγRIIa subtype								
RR	21	–3.0 (1.6)	15	–2.3 (1.7)	9	–3.0 (1.0)	24	–2.6 (1.5)
HR+HH	95	–2.9 (1.2)	101	–2.9 (1.4)	38	–3.0 (1.4)	139	–2.9 (1.4)
FcγRIIIa subtype								
FF	62	–2.9 (1.3)	49	–2.9 (1.5)	22	–3.3 (1.4)	71	–3.0 (1.5)
FV+VV	48	–3.0 (1.3)	66	–2.8 (1.4)	24	–2.7 (1.2)	90	–2.7 (1.3)
DAS28-CRP								
Week 24								
FcγRIIa subtype								
RR	23	–2.3 (1.2)	15	–1.7 (1.2)	9	–2.4 (0.8)	24	–2.0 (1.1)
HR+HH	98	–2.4 (1.0)	108	–2.4 (1.1)	40	–2.2 (1.4)	148	–2.4 (1.2)

FcγRIIIa subtype								
FF	66	–2.4 (1.2)	53	–2.2 (1.3)	23	–2.5 (1.3)	76	–2.3 (1.3)
FV+VV	49	–2.3 (1.2)	69	–2.4 (1.0)	25	–2.0 (1.3)	94	–2.3 (1.1)
Week 48								
FcγRIIa subtype								
RR	21	–2.6 (1.3)	15	–2.3 (1.7)	9	–2.8 (0.8)	24	–2.4 (1.4)
HR+HH	94	–2.7 (1.1)	100	–2.6 (1.3)	38	–2.7 (1.4)	138	–2.7 (1.3)
FcγRIIIa subtype								
FF	62	–2.6 (1.0)	49	–2.6 (1.3)	22	–3.0 (1.4)	71	–2.7 (1.4)
FV+VV	47	–2.7 (1.3)	65	–2.6 (1.3)	24	–2.4 (1.2)	89	–2.5 (1.3)

CRP C-reactive protein, *DAS28* Disease Activity Score using 28 joints, *ESR* erythrocyte sedimentation rate, *EU* European Union, *FcγR* Fc gamma receptor, *RTX* rituximab, *SD* standard deviation, *US* United States

[a]Week 48 data are from the efficacy population–2nd treatment course subset (CT-P10, n=139; US-RTX, n=135; EU-RTX, n=53; Combined RTX, n=193). [b]US-RTX and EU-RTX groups combined.

Table S3 Secondary pharmacokinetic parameters up to Week 48 (PK population)

Parameter (unit)	**CT-P10**	**US-RTX**	**EU-RTX**
(PK population)	**n=154**	**n=147**	**n=59**
$C_{max\ 1st\ course}$ (µg/mL), n	151	146	59
Mean (CV)	438.0 (24.2)	432.6 (27.5)	474.2 (21.2)
$C_{max\ 1,\ 1st\ course}$ (µg/mL), n	153	146	59
Mean (CV)	361.6 (25.1)	373.8 (21.9)	394.3 (20.2)
$C_{min\ W24}$ (µg/mL), n	136	135	56
Mean (CV)	6.0 (716.1)	6.0 (635.9)	0.5 (162.2)
$C_{trough\ 1st\ course}$ (µg/mL)	153	146	59
Mean (CV)	75.4 (68.4)	84.7 (80.8)	81.8 (67.3)
$T_{max\ 1st\ course}$ (h)	153	147	59
Median (min, max)	339.7 (4.3, 557.0)	339.6 (4.5, 367.3)	339.3 (4.5, 346.5)
(PK population -2nd treatment course subset)	**n=141**	**n=137**	**n=57**
$C_{max\ 2nd\ course}$ (µg/mL), n	141	137	57
Mean (CV)	418.9 (29.3)	420.3 (29.5)	464.5 (23.9)
$C_{max\ 1,\ 2nd\ course}$ (µg/mL), n	141	136	57
Mean (CV)	353.0 (25.8)	350.3 (27.9)	382.2 (23.1)
$C_{min\ W48}$ (µg/mL), n	138	132	55
Mean (CV)	4.4 (784.2)	1.0 (169.8)	2.1 (354.5)

$C_{trough\ 2nd\ course}$ (µg/mL), n	141	136	57
Mean (CV)	83.0 (76.2)	80.1 (51.7)	88.3 (51.2)
$T_{max\ 2nd\ course}$ (h)	141	137	57
Median (min, max)	339.8 (0.0, 4152.2)	339.9 (4.3, 4125.0)	339.7 (4.6, 411.8)

$C_{max\ 1st\ course}$ maximum concentration after the second infusion in the 1st treatment course, $C_{max\ 1,\ 1st\ course}$ maximum concentration after the first infusion in the 1st treatment course, $C_{max\ 2nd\ course}$ maximum concentration after the second infusion in the 2nd treatment course, $C_{max\ 1,\ 2nd\ course}$ maximum concentration after the first infusion in the 2nd treatment course, $C_{min\ W24}$ predose concentration at Day 168 (Week 24), $C_{min\ W48}$ predose concentration at Day 336 (Week 48), $C_{trough\ 1st\ course}$ predose concentration at Day 14 (Week 2 prior to second infusion), $C_{trough\ 2nd\ course}$ predose concentration at Day 182 (Week 26 prior to second infusion), *CV* coefficient of variation, *EU* European Union, *PK* pharmacokinetic, *RTX*=rituximab, $T_{max\ 1st\ course}$ time to maximum concentration in the 1st treatment course, $T_{max\ 2nd\ course}$ time to maximum concentration in the 2nd treatment course, *US* United States

Table S4 Adverse events reported in >3% of patients in any group (safety population)

System organ class Preferred term	CT-P10 (n=161)	US-RTX (n=151)	EU-RTX (n=60)	Combined RTX (n=211)	Total (n=372)
	Number (%) of patients				
Total number of AEs	350	294	96	390	740
Total patients with ≥1 AE	125 (77.6)	97 (64.2)	39 (65.0)	136 (64.5)	261 (70.2)
Infections and infestations	**62 (38.5)**	**54 (35.8)**	**17 (28.3)**	**71 (33.6)**	**133 (35.8)**
Upper respiratory tract infection	24 (14.9)	30 (19.9)	9 (15.0)	39 (18.5)	63 (16.9)
Urinary tract infection	15 (9.3)	8 (5.3)	2 (3.3)	10 (4.7)	25 (6.7)
Lower respiratory tract infection	10 (6.2)	8 (5.3)	3 (5.0)	11 (5.2)	21 (5.6)
Rhinitis	3 (1.9)	6 (4.0)	1 (1.7)	7 (3.3)	10 (2.7)
Influenza	2 (1.2)	0 (0.0)	2 (3.3)	2 (0.9)	4 (1.1)
Injury, poisoning, and procedural complications	**43 (26.7)**	**23 (15.2)**	**14 (23.3)**	**37 (17.5)**	**80 (21.5)**
Infusion-related reaction	33 (20.5)	12 (7.9)	13 (21.7)	25 (11.8)	58 (15.6)
Fracture	4 (2.5)	6 (4.0)	1 (1.7)	7 (3.3)	11 (3.0)
Injury	4 (2.5)	5 (3.3)	0 (0.0)	5 (2.4)	9 (2.4)
Gastrointestinal disorders	**17 (10.6)**	**19 (12.6)**	**7 (11.7)**	**26 (12.3)**	**43 (11.6)**

Abdominal pain	4 (2.5)	5 (3.3)	1 (1.7)	6 (2.8)	10 (2.7)
Musculoskeletal and connective tissue disorders	**20 (12.4)**	**14 (9.3)**	**5 (8.3)**	**19 (9.0)**	**39 (10.5)**
Back pain	5 (3.1)	4 (2.6)	1 (1.7)	5 (2.4)	10 (2.7)
Investigations	**18 (11.2)**	**16 (10.6)**	**3 (5.0)**	**19 (9.0)**	**37 (9.9)**
Alanine aminotransferase increased	5 (3.1)	7 (4.6)	0 (0.0)	7 (3.3)	12 (3.2)
Nervous system disorders	**14 (8.7)**	**13 (8.6)**	**2 (3.3)**	**15 (7.1)**	**29 (7.8)**
Headache	8 (5.0)	8 (5.3)	2 (3.3)	10 (4.7)	18 (4.8)
Metabolism and nutrition disorders	**16 (9.9)**	**10 (6.6)**	**2 (3.3)**	**12 (5.7)**	**28 (7.5)**
Hypertriglyceridemia	7 (4.3)	4 (2.6)	1 (1.7)	5 (2.4)	12 (3.2)
Skin and subcutaneous tissue disorders	**11 (6.8)**	**9 (6.0)**	**4 (6.7)**	**13 (6.2)**	**24 (6.5)**
Pruritus[a]	3 (1.9)	1 (0.7)	3 (5.0)	4 (1.9)	7 (1.9)
Blood and lymphatic system disorders	**10 (6.2)**	**10 (6.6)**	**4 (6.7)**	**14 (6.6)**	**24 (6.5)**
Anemia	6 (3.7)	5 (3.3)	2 (3.3)	7 (3.3)	13 (3.5)
Vascular disorders	**8 (5.0)**	**7 (4.6)**	**0 (0.0)**	**7 (3.3)**	**15 (4.0)**
Hypertension	6 (3.7)	4 (2.6)	0 (0.0)	4 (1.9)	10 (2.7)
Psychiatric disorders	**4 (2.5)**	**4 (2.6)**	**3 (5.0)**	**7 (3.3)**	**11 (3.0)**
Depression	1 (0.6)	1 (0.7)	2 (3.3)	3 (1.4)	4 (1.1)

AE adverse event, *EU* European Union, *RTX* rituximab, *US* United States

Note: The total number of AEs included all patient events. At each level of summarization, a patient was counted only once if they reported one or more events. Only the most severe event was counted.

System organ classes were arranged by decreasing total percentage, and system organ class and combined preferred terms were coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 18.1

[a]Out of the seven pruritus cases, five cases occurred at least two weeks after the last infusion date of study drug. Two pruritus cases (both from the CT-P10 group) occurred within two weeks after the last infusion date of study drug, but both cases were considered unrelated to the study drug by the investigator.

Table S5 Serious adverse events reported in any group (safety population)

System organ class Preferred term	CT-P10 (n=161)	US-RTX (n=151)	EU-RTX (n=60)	Combined RTX (n=211)	Total (n=372)
	Number (%) of patients				
Total number of SAEs	**14**	**16**	**4**	**20**	**34**
Total patients with at least 1 SAE	**13 (8.1)**	**14 (9.3)**	**4 (6.7)**	**18 (8.5)**	**31 (8.3)**
Injury, poisoning, and procedural complications	**4 (2.5)**	**4 (2.6)[a]**	**0 (0.0)**	**4 (1.9)**	**8 (2.2)**
Fracture	4 (2.5)	2 (1.3)	0 (0.0)	2 (0.9)	6 (1.6)
Injury	0 (0.0)	2 (1.3)	0 (0.0)	2 (0.9)	2 (0.5)
Joint dislocation	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.5)	1 (0.3)
Infections and infestations	**2 (1.2)**	**4 (2.6)**	**0**	**4 (1.9)**	**6 (1.6)**
Cellulitis	1 (0.6)	1 (0.7)[b]	0 (0.0)	1 (0.5)	2 (0.5)
Localized infection	0 (0.0)	1 (0.7)[b]	0 (0.0)	1 (0.5)	1 (0.3)
Lower respiratory tract infection	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.5)	1 (0.3)
Pneumonia	1 (0.6)	1 (0.7)[b]	0 (0.0)	1 (0.5)	2 (0.5)
Blood and lymphatic system disorders	**1 (0.6)**	**1 (0.7)**	**1 (1.7)**	**2 (0.9)**	**3 (0.8)**
Leukopenia	0 (0.0)	0 (0.0)	1 (1.7)[b]	1 (0.5)	1 (0.3)
Pancytopenia	1 (0.6)	1 (0.7)[b]	0 (0.0)	1 (0.5)	2 (0.5)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	**0 (0.0)**	**2 (1.3)**	**3 (5.0)**	**5 (2.4)**	**5 (1.3)**

Adenocarcinoma of colon	0 (0.0)	0 (0.0)	1 (1.7)	1 (0.5)	1 (0.3)
Bladder cancer	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.5)	1 (0.3)
Breast cancer	0 (0.0)	1 (0.7)	1 (0.7)	2 (0.9)	2 (0.5)
Lymphangioma	0 (0.0)	0 (0.0)	1 (1.7)	1 (0.5)	1 (0.3)
Gastrointestinal disorders	**0 (0.0)**	**2 (1.3)**	**0 (0.0)**	**2 (0.9)**	**2 (0.5)**
Colitis ischemic	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.5)	1 (0.3)
Intestinal obstruction	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.5)	1 (0.3)
Hepatobiliary disorders	**2 (1.2)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**2 (0.5)**
Cholecystitis	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Cholelithiasis	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Musculoskeletal and connective tissue disorders	**1 (0.6)**	**1 (0.7)**	**0 (0.0)**	**1 (0.5)**	**2 (0.5)**
Arthralgia	0 (0.0)	1 (0.7)[b]	0 (0.0)	1 (0.5)	1 (0.3)
Hand deformity	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Nervous system disorders	**1 (0.6)**	**1 (0.7)**	**0 (0.0)**	**1 (0.5)**	**2 (0.5)**
Tremor	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Vertebrobasilar insufficiency	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.5)	1 (0.3)
General disorders and administration site conditions	**1 (0.6)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.3)**
Chest pain	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Renal and urinary disorders	**1 (0.6)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.3)**
Acute kidney injury	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Respiratory, thoracic and mediastinal disorders	**1 (0.6)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.3)**
Dyspnea exertional	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

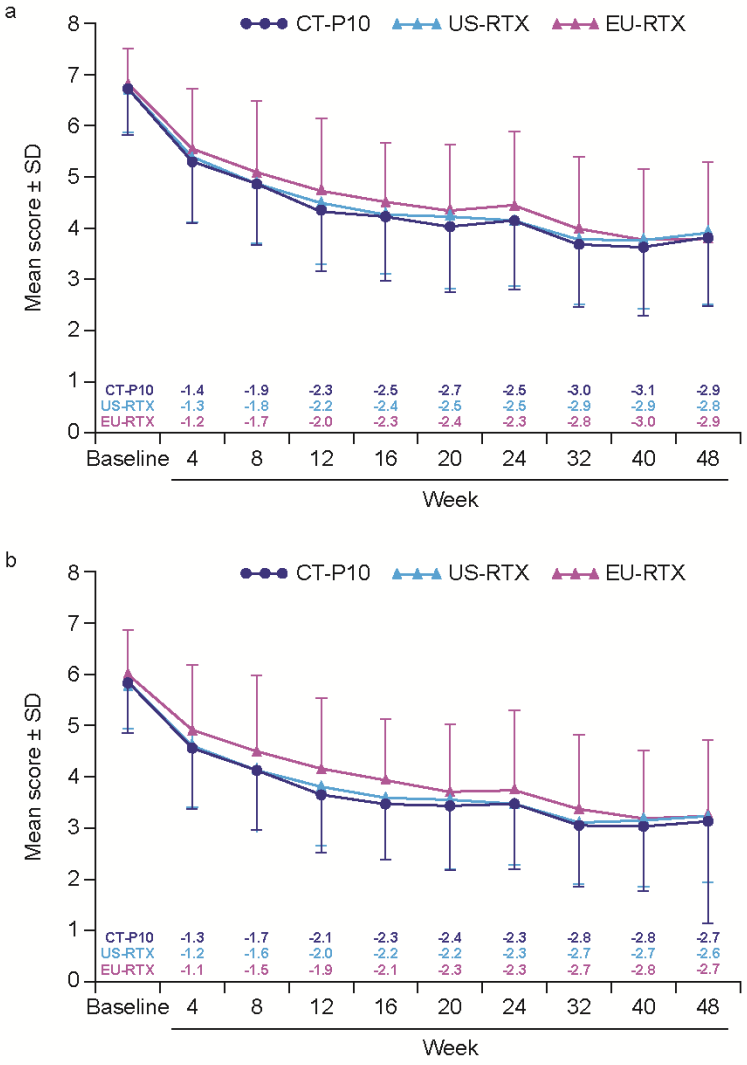
EU European Union, *RTX* rituximab, *SAE* serious adverse event, *US* United States

Note: The total number of AEs included all patient events. At each level of summarization, a patient was counted only once if they reported one or more events. Only the most severe event was counted. System organ classes were arranged by decreasing total percentage, and system organ class and combined preferred terms were coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 18.1.

[a]One patient had 2 SAEs (fracture and joint dislocation). [b]Cases related to the study drug.

Fig. S1 Mean change from baseline in disease activity

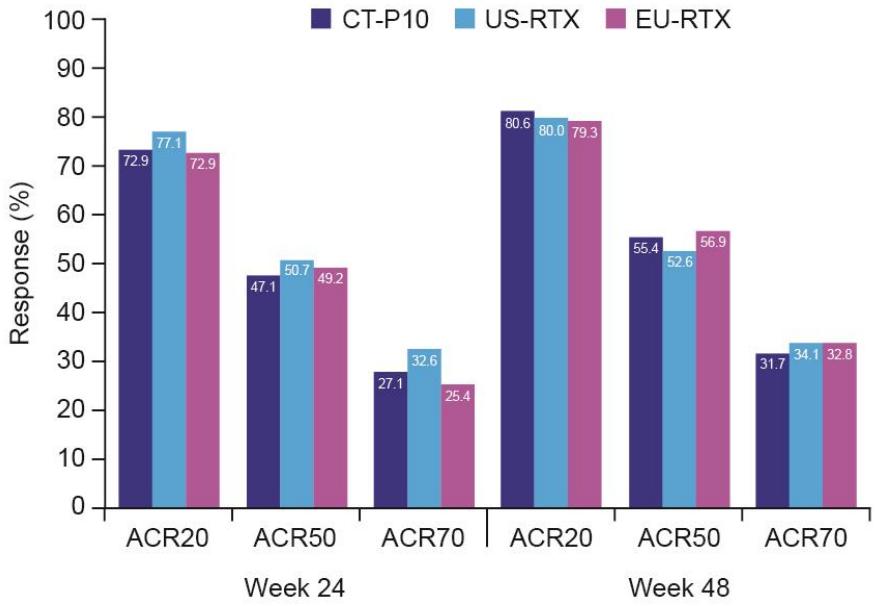
(a) DAS28-ESR, (b) DAS28-CRP over 48 weeks in the CT-P10, US-RTX and EU-RTX groups (efficacy population [a]).



CRP C-reactive protein, *DAS28* Disease Activity Score using 28 joint counts, *ESR* erythrocyte sedimentation rate, *EU* European Union, *RTX* rituximab, *SD* standard deviation, *US* United States

[a] Data after Week 24 are from the efficacy population–2nd treatment course subset.

Fig. S2 Proportion of patients achieving clinical response at 24 and 48 weeks (efficacy population[a])



ACR American College of Rheumatology, *EU* European Union, *RTX* rituximab, *US* United States

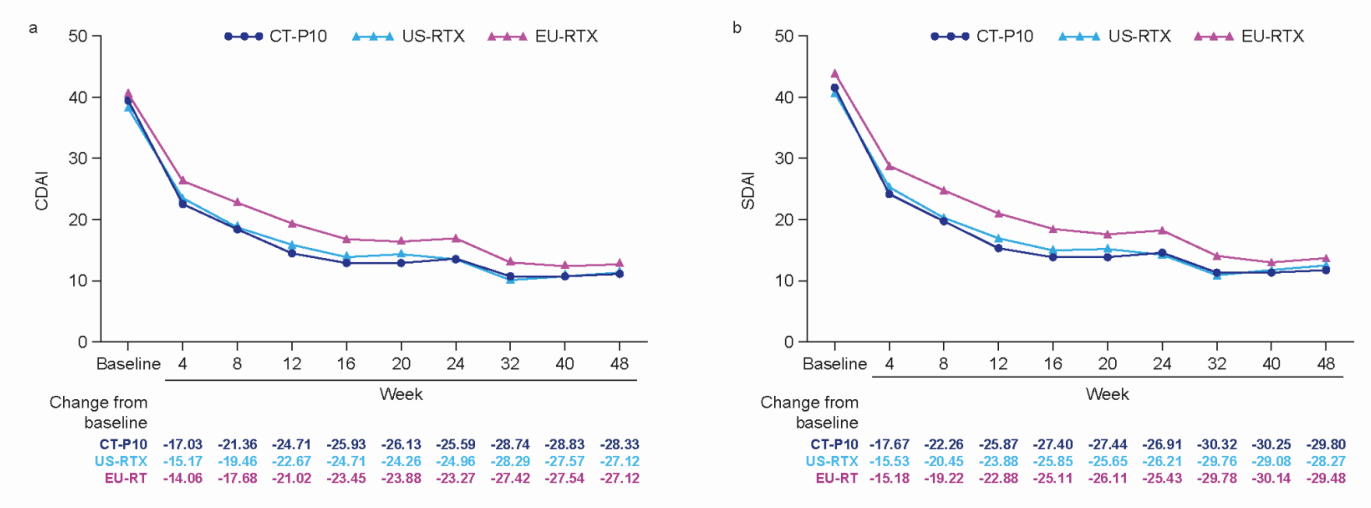
[a]Week 48 data are from the efficacy population–2nd treatment course subset.

Fig. S3 EULAR response at Weeks 24 and 48 (efficacy population [a])

EULAR European League Against Rheumatism, *RTX* rituximab

[a]Week 48 data are from the efficacy population–2nd treatment course subset.

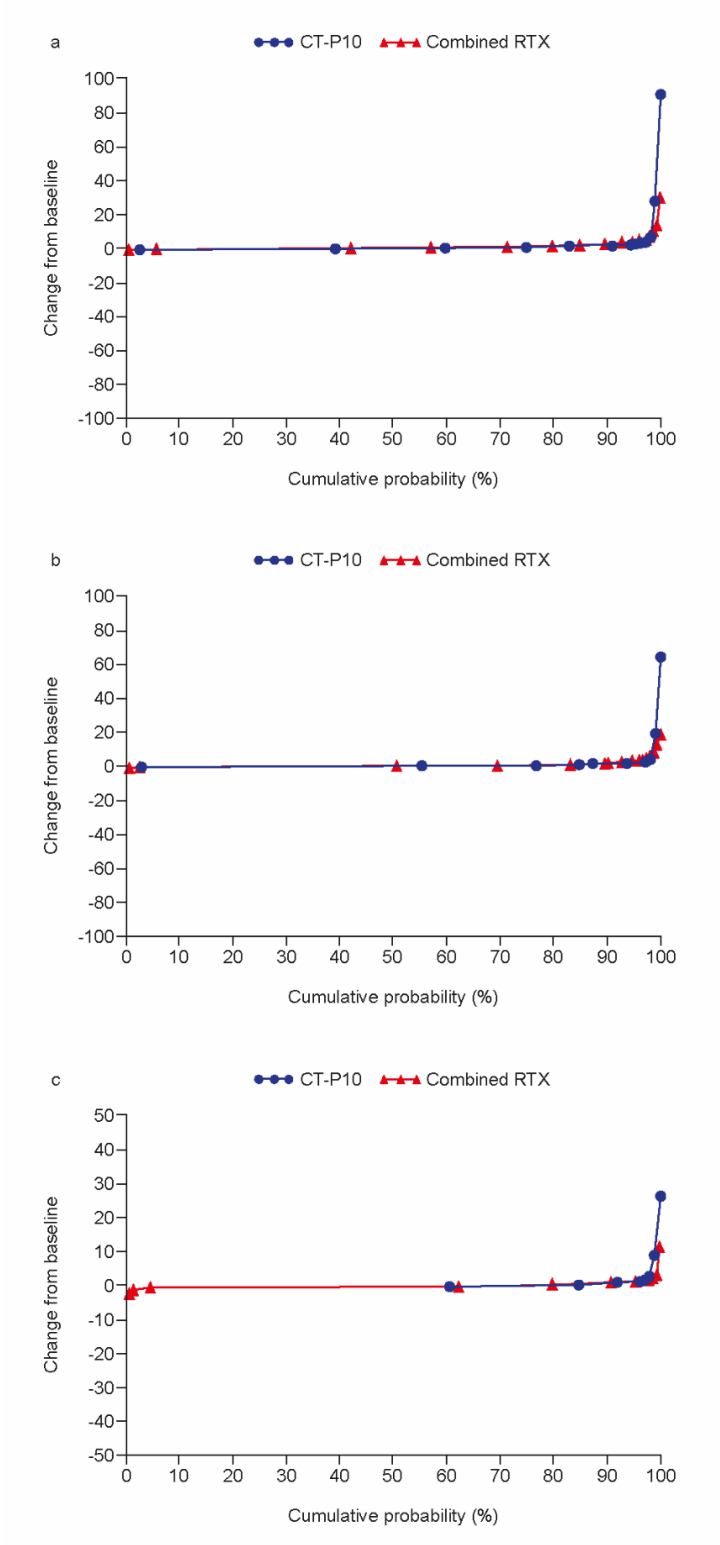
Fig. S4 Mean clinical disease activity index (CDAI) score (a) and mean simplified disease activity index (SDAI) score (b) (efficacy population [a])



CDAI clinical disease activity index, *EU* European Union, *RTX* rituximab, *SDAI* simplified disease activity index, US=United States

[a]Week 32, week 40, and week 48 data are from the efficacy population–2nd treatment course subset.

Fig. S5 Cumulative probability distribution of joint damage progression (efficacy population) (a) total score, (b) Total erosion score, (c) Total JSN score.



JSN joint space narrowing, *RTX* rituximab