Supplementary Table 1: Summary of all adverse events (Safety set*)

	ABX464 100mg (N=19)	ABX464 50mg (N=21)	Placebo (N=20)	Total (N=60)
	n N (%)	n N (%)	n N (%)	n N (%)
Any Adverse Event	97 18 (94.7%)	85 18 (85.7%)	38 14 (70.0%)	220 50 (83.3%)
Any Treatment-Emergent Adverse Event	94 18 (94.7%)	79 18 (85.7%)	38 14 (70.0%)	211 50 (83.3%)
Chi-squared test, ABX464 vs. placebo p-value	0.035	0.221		
Any Serious Adverse Event	1 1 (5.3%)	1 1 (4.8%)	1 1 (5.0%)	3 3 (5.0%)
Adverse Event leading to death	0	0	0	0
Any grade 3 or higher Adverse Event	4 3 (15.8%)	3 3 (14.3%)	1 1 (5.0%)	8 7 (11.7%)
Atrial fibrillation	1 (5.3%)	0	0	1 (1.7%)
Abdominal pain upper	1 (5.3%)	0	0	1 (1.7%)
Diarrhoea	1 (5.3%)	0	0	1 (1.7%)
COVID-19	0	0	1 (5.0%)	1 (1.7%)
Disturbance in attention	0	1 (4.8%)	0	1 (1.7%)
Headache	1 (5.3%)	0	0	1 (1.7%)
Organic brain syndrome	0	1 (4.8%)	0	1 (1.7%)

N (%): number and percentage of patients ; n: number of events. The denominator for each percentage is the number of patients within the column. Treatment emergent adverse event rate for ABX464 vs placebo is compared using likelihood ratio chi-square test at a two-sided 10% significance level.

*: the safety set corresponded to included patients who had received at least one dose of the study treatment.

Supplementary Table 2: TEAEs leading to drug discontinuation, by SOC and Preferred Term (Safety set)

	ABX464 100mg (N=19)		ABX464 50mg (N=21)		Placebo (N=20)	
	n	N (%)	n	N (%)	n	N (%)
Number of patients withdrawn for AEs	9		1		1	
Any TEAEs Leading to permanent Study Drug Discontinuation	17	9 (47.4%)	1	1 (4.8%)	1	1 (5.0%)
Cardiac disorders	1	1 (5.3%)	0	0	0	0
Atrial fibrillation	1	1 (5.3%)	0	0	0	0
Gastrointestinal disorders	11	9 (47.4%)	1	1 (4.8%)	0	0
Abdominal pain	1	1 (5.3%)	0	0	0	0
Abdominal pain upper	2	2 (10.5%)	1	1 (4.8%)	0	0
Diarrhoea	3	3 (15.8%)	0	0	0	0
Nausea	4	4 (21.1%)	0	0	0	0
Vomiting	1	1 (5.3%)	0	0	0	0
Infections and infestations	0	0	0	0	1	1 (5.0%)
COVID-19	0	0	0	0	1	1 (5.0%)
Musculoskeletal and connective tissue disorders	1	1 (5.3%)	0	0	0	0
Arthralgia	1	1 (5.3%)	0	0	0	0
Nervous system disorders	4	4 (21.1%)	0	0	0	0
Headache	4	4 (21.1%)	0	0	0	0

n: number of events; N(%): number and percentage of patients. The denominator for each percentage is the number of patients within the column. Duration (days) represents median duration of AEs (from baseline to occurrence). AE = adverse event; SOC: system organ class.

*: the safety set corresponded to included patients who had received at least one dose of the study treatment.

Supplementary Table 3: Haematology and biochemistry median changes (and min-max values) from baseline to week 12 (Safety set)

		ABX464 100mg	ABX464 50mg	Placebo
Haematology				
ESR (mm/h)	n	7	16	18
		-1.0 (-22 ; 18)	-5.0 (-37; 49)	-2.5 (-38; 41)
Hemoglobin (g/L)	n	7	18	19
		5.0 (0; 13)	-1.0 (-17; 16)	-1.0 (-11; 11)
White blood cells (x10^9/L)	n	7	18	19
		0.90 (-1.5; 3.3)	1.35 (-2.1; 5.1)	-0.40 (-3.2; 4.8)
Neutrophils (x10^9/L)	n	7	18	19
		0.700 (-1.81; 2.66)	0.864 (-2.40; 5,40)	-0.140 (-2.29; 4.62)
Lymphocytes (x10^9/L)	n	7	18	19
		0.030 (-1.77; 0.61)	0.435 (-0.28; 1.12)	-0.007 (-0.77; 0.93)
Monocytes (x10^9/L)	n	7	18	19
		0.220 (-0.27; 0.28)	0.188 (-0.10; 0.41)	-0.030 (-0.20; 0.21)
Eosinophils (x10^9/L)	n	7	18	19
		0.000 (-0.09; 0.20)	0.035 (-0.18; 0.23)	-0.010 (-0.20; 0.15)
Basophils (x10^9/L)	n	7	18	19
		-0.010 (-0.05; 0.05)	0.009 (-0.04; 0.04)	0.000 (-0.04; 0.12)
Platelet Count (x10^9/L)	n	7	18	19
		-64.0 (-429; -28)	-18.5 (-121; 379)	-8.0 (-149; 35)
Fibrinogen (g/L)	n	7	15	15
		0.571 (-0.29; 1.44)	0.520 (-2.07; 2.22)	-0.035 (-1.68; 1.26)
Biochemistry				
CRP (mg/L)	n	7	18	19
		0.00 (-8.8; 13.4)	-3.60 (-54.9; 87.5)	-1.70 (-36.3; 65.5)
Creatinine (µmol/L)	n	7	18	18
		0.00 (-10.6; 22.1)	-0.44 (-20.3; 12.0)	0.00 (-48.6; 9.7)
Aspartate Aminotransferase (U/L)	n	7	18	19
		5.00 (-1.3; 14.0)	-0.05 (-30; 9.0)	1.00 (-15.0; 18.5)
Alanine Aminotransferase (U/L)	n	7	18	19
		11.00 (0.1; 19.0)	-0.50 (-42.0; 9.4)	0.20 (-20.0; 8.9)
Lipase (U/L)	n	6	18	17
		1.50 (-34.3; 28.0)	7.14 (-19.0; 41.0)	0.00 (-15.7; 17.9)
HDL cholesterol (mmol/L)	n	7	18	19
		-0.181 (-0.65; 0.04)	-0.223 (-0.60; 0.18)	-0.034 (-1.13; 0.54)
LDL cholesterol (mmol/L)	n	7	18	19
		0.329 (-0.68; 1.94)	0.167 (-0.15; 2.01)	-0.018 (-1.56; 0.99)
Bilirubin (µmol/L)	n	7	18	19
		0.68 (-2.7; 9.1)	-0.17 (-4.0; 4.1)	1.03 (-9.6; 5.6)

Supplementary Table 4: Changes from baseline at week 12 in ESR, DAS28-CRP, DAS28-ESR, SDAI, CDAI, HAQ-DI and FACIT-Fatigue (PP Set)

		ABX464 100 mg (N=18)	ABX464 50 mg (N=20)	Placebo (N=20)
ESR	N	7 (38.9%)	15 (75.0%)	18 (90.0%)
	Mean (SD)	-0.9 (11.7)	-3.5 (23.0)	-3.0 (17.5)
	95% CI	-12 to 10	-16 to 9	-12 to 6
	Min – Max	-22 to 18	-37 to 49	-38 to 41
	p-value*	0.769	0.940	
DAS28-CRP	N	7 (38.9%)	16 (80.0%)	19 (95.0%)
	Mean (SD)	-1.94 (1.03)	-1.79 (-1.44)	-0.63 (0.99)
	95% CI	-2.9 to -1.0	-2.6 to -1.0	-1.1 to -0.1
	Min – Max	-3.3 to -0.4	-4.8 to 0.1	-3.3 to 0.6
	p-value*	0.006	**0.008**	
DAS28-ESR	N	7 (38.9%)	14 (70.0%)	18 (90.0%)
	Mean (SD)	-2.0 (0.8)	-1.8 (1.4)	-0.6 (1.0)
	95% CI	-2.8 to -1.2	-2.7 to -1.0	-1.2 to -0.1
	Min – Max	-3.1 to -0.9	-4.5 to -0.2	-3.5 to 0.6
	p-value*	**0.006**	**0.010**	
SDAI	N	7 (38.9%)	16 (80.0%)	19 (95.0%)
	Mean (SD)	-25.4 (12.2)	-22.6 (35.1)	-7.9 (23.2)
	95% CI	-36.7 to -14.2	-41.4 to -3.9	-19.2 to 3.2
	Min – Max	-39.5 to -7.0	-85.2 to 62.7	-44.5 to 63.1
	p-value*	0.072	0.149	
CDAI	N	7 (38.9%)	16 (80.0%)	19 (95.0%)
	Mean (SD)	-27.1 (14.5)	-20.2 (12.0)	-7.3 (10.2)
	95% CI	-40.6 to -13.7	-26.6 to -13.8	-12.2 to -2.3
	Min – Max	-51.1 to -9.4	-48.0 to -3.5	-26.0 to 9.0
	p-value*	**0.0007**	**0.001**	
SJC	N	7 (38.9%)	16 (80.0%)	19 (95.0%)
	Mean (SD)	-8.6 (5.4)	-5.8 (4.0)	-2.2 (4.3)
	95% CI	-14.0 to -4.0	-8.0 to -4.0	-4.0 to -0.0
	Min – Max	-18.0 to -3.0	-12.0 to 1.0	-12.0 to 5.0
	p-value*	**0.004**	**0.017**	
TJC	N	7 (38.9%)	16 (80.0%)	19 (95.0%)
	Mean (SD)	-11.0 (6.5)	-8.6 (6.2)	-3.0 (3.8)
	95% CI	-17.0 to -5.0	-12.0 to -5.0	-5.0 to -1.0
	Min – Max	-24.0 to -3.0	-24.0 to -1.0	-11.0 to 4.0
	p-value*	**0.0007**	**0.002**	
CRP	N	7 (38.9%)	17 (85.0%)	19 (95.0%)
	Mean (SD)	1.6 (8.3)	-2.2 (29.8)	-0.6 (19.2)
	95% CI	-6.0 to 9.4	-17.6 to 13.1	-10.0 to 8.6
	Min – Max	-8.8 to 13.4	-54.9 to 87.5	-36.3 to 65.5
	p-value*	0.757	0.848	
Pain-VAS	N	7 (38.9%)	17 (85.0%)	19 (95.0%)
	Mean (SD)	-2.4 (2.7)	-3.0 (2.4)	-0.8 (2.4)
	95% CI	-4.9 to 0.1	-4.3 to -1.8	-2.0 to 0.3

	Min – Max	-8.2 to -0.6	-7.3 to -0.1	-7.0 to 3.6
	p-value*	0.159	**0.008**	
HAQ-DI	N	7 (38.9)	17 (85.0%)	19 (95.0%)
	Mean (SD)	-0.28 (0.54)	-0.50 (0.66)	-0.19 (0.49)
	95% CI	-0.78 to 0.21	-0.84 to -0.16	-0.42 to 0.04
	Min – Max	-1.37 to 0.37	-1.75 to 0.62	-1.75 to 0.87
	p-value*	0.675	0.110	
FACIT-Fatigue	N	7 (38.9%)	17 (85.0%)	19 (95.0%)
	Mean (SD)	7.9 (11.0)	7.5 (6.0)	3.2 (6.4)
	95% CI	-2 to 18	4 to 11	0 to 6
	Min – Max	-4 to 26	0 to 20	-11 to 15
	p-value*	0.191	**0.045**	

CDAI = clinical disease activity score; CI = confidence interval; CRP = C-reactive protein; DAS =disease activity score; ESR = erythrocyte sedimentation rate; FACIT = functional assessment of chronic illness therapy; max = maximum; min = minimum; SD = standard deviation; HAQ-DI: Healthy Assessment Questionnaire - Disability Index; SDAI = simplified disease activity score.

*: Analysis of Covariance, ABX-464 vs placebo; Mixed model Analysis of Covariance is conducted for the changes from baseline for each parameter.

Supplementary Table 5: Patients' responses and remissions at week 12 (PP Set)

		ABX464 100 mg (N=18)	ABX464 50 mg (N=20)	Placebo (N=20)
ACR/EULAR Boolean Remission	N	7	16	19
	Yes	0	1 (6.3%)	0
	95% CI	59.0 to 100.0	0.2 to 30.2	82.4 to 100.0
	p-value*	NC	0.2058	
ACR20 Response	N	7	16	19
	Yes	3 (42.9%)	9 (56.3%)	4 (21.1%)
	95% CI	9.9 to 81.6	29.9 to 80.2	6.1 to 45.6
	p-value*	0.2790	**0.0303**	
ACR50 Response	N	7	16	19
	Yes	2 (28.6%)	5 (31.3%)	1 (5.3%)
	95% CI	3.7 to 71.0	11.0 to 58.7	0.1 to 26.0
	p-value*	0.122	**0.036**	
ACR70 Response	N	7	16	19
	Yes	1 (14.3%)	4 (25.0%)	1 (5.3%)
	95% CI	0.4 to 57.9	7.3 to 52.4	0.1 to 26.0
	p-value*	0.468	0.089	
Categorical DAS28-CRP Response	N	7	16	19
	Yes	6 (85.7%)	14 (87.5%)	8 (42.1%)
	95% CI	42.1 to 99.6	61.7 to 98.4	20.3 to 66.5
	p-value*	**0.038**	**0.004**	
DAS28-ESR Remission	N	7	14	18
	Yes	0	2 (14.3%)	0
	95% CI	59.0 to 100.0	1.8 to 42.8	81.5 to 100.0
	p-value*	NC	0.062	
Low Disease Activity (LDA)	N	7	14	18
	Yes	2 (28.6%)	3 (21.4%)	2 (11.1%)
	95% CI	3.7 to 71.0	4.7 to 50.8	1.4 to 34.7
	p-value*	0.305	0.426	
SDAI Remission	N	7	16	19
	Yes	0	1 (6.3%)	0
	95% CI	59.0 to 100.0	0.2 to 30.2	82.4 to 100.0
	p-value*	NC	0.205	
CDAI Remission	N	7	16	19
	Yes	0	3 (18.8%)	0
	95% CI	59.0 to 100.0	4.0 to 45.6	82.4 to 100.0
	p-value*	NC	**0.024**	

ACR = American College of Rheumatology; CDAI = clinical disease activity score; CI = confidence interval; DAS =disease activity score; ESR = erythrocyte sedimentation rate; EULAR = European League Against Rheumatism; LDA = low disease activity; SDAI = simplified disease activity score. *: Chi-squared test ABX-464 vs. placebo. NC - No statistics from Chi Square test produced because response has fewer than 2 non missing levels.

Supplementary Table 6: ACR20, ACR50, and ACR70 response rates at week 12 in subsets of patients exposed or not to anti-TNFα (ITT Set)

		ABX464 100 mg (N=19)	ABX464 50 mg (N=21)	Placebo (N=20)
ACR20 Response				
w/out anti-TNF exp.	N	13	15	14
	n (%)	1 (7.7)	7(46.5)	3 (21.4)
with anti-TNF exp	N	6	6	6
	n (%)	2 (33.3)	2 (33.3)	1 (16.7)
ACR50 Response				
w/out anti-TNF exp.	N	13	15	14
	n (%)	1 (7.7)	4 (26.7)	1 (7.1)
with anti-TNF exp	N	6	6	6
	n (%)	1 (16.7)	1 (16.7)	0 (0)
ACR70 Response				
w/out anti-TNF exp.	N	13	15	14
	n (%)	1 (7.7)	3 (20)	1 (7.1)
with anti-TNF exp	N	6	6	6
	n (%)	0 (0)	1 (16.7)	0 (0)

Supplementary Table 7: Changes from baseline at week 12 in ESR, DAS28-CRP, DAS28-ESR, SDAI, CDAI and FACIT-Fatigue (Efficacy Set 2†)

		ABX464 100 mg (N=19)	ABX464 50 mg (N=21)	Placebo (N=20)
ESR	N	12	19	20
	Mean (SD)	-5.9 (16.7)	0.5 (23.2)	-4.6 (18.1)
	95% CI	-17 to 5	-11 to 12	-13 to 4
	p-value*	0.832	0.449	
DAS28-CRP	N	12	19	20
	Mean (SD)	-1.5 (1.0)	-1.6 (1.3)	-0.6 (0.9)
	95% CI	-2.1 to -0.9	-2.3 to -1.0	-1.1 to -0.2
	p-value*	0.021	0.009	
DAS28-ESR	N	12	19	20
	Mean (SD)	-1.5 (0.9)	-1.6 (1.3)	-0.6 (0.9)
	95% CI	-2.1 to -0.9	-2.3 to -1.0	-1.1 to -0.2
	p-value*	**0.019**	0.011	
SDAI	N	12	19	20
	Mean (SD)	-30.7 (33.9)	-23.0 (33.9)	-8.2 (22.6)
	95% CI	-52.3 to -9.1	-39.4 to -6.7	-18.9 to 2.3
	p-value*	**0.032**	0.116	
CDAI	N	12	19	20
	Mean (SD)	-20.3 (14.4)	-18.4 (11.8)	-7.4 (10.0)
	95% CI	-29.5 to -11.1	-24.1 to -12.7	-12.1 to -2.7
	p-value*	**0.005**	**0.003**	
FACIT-Fatigue	N	12	19	20
	Mean (SD)	6.6 (9.2)	6.6 (6.5)	3.7 (6.6)
	95% CI	1 to 12	3 to 10	1 to 7

CDAI = clinical disease activity score; CI = confidence interval; CRP = C-reactive protein; DAS =disease activity score; ESR = erythrocyte sedimentation rate; FACIT = functional assessment of chronic illness therapy; max = maximum; min = minimum; SD = standard deviation; SDAI = simplified disease activity score.

*: Analysis of Covariance, ABX-464 vs placebo; Mixed model Analysis of Covariance is conducted for the changes from baseline for each parameter.

†: The efficacy Set 2 used data imputation (last observation carried forward) from Week 4 onwards. If there were no efficacy data available, then the dropout was considered as treatment failure.

Supplementary Table 8: Patients' responses and remissions at week 12 (Efficacy Set 2†)

		ABX464 100 mg (N=19)	ABX464 50 mg (N=21)	Placebo (N=20)
ACR20 Response	N	12	19	20
	Yes	33.3%	47.4%	20.0%
	95% CI	9.9 to 65.1	24.4 to 71.1	5.7 to 43.7
ACR50 Response	N	12	19	20
	Yes	16.7%	26.3%	5.0%
	95% CI	2.1 to 48.4	9.1 to 51.2	0.1 to 24.9
ACR70 Response	N	12	19	20
	Yes	8.3%	21.1%	5.0%
	95% CI	0.2 to 38.5	6.1 to 45.6	0.1 to 24.9
Categorical DAS28-CRP Response	N	12	19	20
	Yes	66.7%	84.2%	45.0%
	95% CI	34.9 to 90.1	60.4 to 96.6	23.1 to 68.5
DAS28-ESR Remission	N	12	19	20
	Yes	0	10.5%	0
	95% CI		1.3 to 33.1	
Low Disease Activity	N	12	19	20
	Yes	16.7%	21.1%	10.0%
	95% CI	2.1 to 48.4	6.1 to 45.6	1.2 to 31.7
SDAI Remission	N	12	19	20
	Yes	0	5.3%	0
	95% CI		0.1 to 26.0	
CDAI Remission	N	12	19	20
	Yes	0	15.8%	0
	95% CI		3.4 to 39.6	
ACR/EULAR Remission	N	12	19	20
	Yes	0	5.3%	0
	95% CI		0.1 to 26.0	

ACR = American College of Rheumatology; CDAI = clinical disease activity score; CI = confidence interval; DAS =disease activity score; ESR = erythrocyte sedimentation rate; EULAR = European League Against Rheumatism; SDAI = simplified disease activity score. *: Chi-squared test ABX-464 vs. placebo. NC - No statistics from Chi Square test produced because response has fewer than 2 non missing levels.

†: The efficacy Set 2 used data imputation (last observation carried forward) from Week 4 onwards. If there were no efficacy data available, then the dropout was considered as treatment failure.

Supplementary Table 9: ABX464 PK parameters by day following administration of 50 mg and 100 mg of ABX464 once a day

ABX464 was rapidly absorbed in patients with RA with a Cmax observed approximately 2 to 3 hours after dosing, which is in the Cmax range measured in healthy volunteers, HIV and UC patients (1.5 to 2.9 hours). Median t_{max} of ABX464 was 2.00 h after administration of ABX464 50 mg of and 2.50-3.00 h after administration of ABX464 100 mg, regardless of the day. Exposure to ABX464 was variable with an inter-individual variability for Cmax and AUC0-t, as expressed by CV%, between 73 and 137%. After repeated administrations of ABX464, an initial decrease in ABX464 AUC is observed and steady state is reached after 8 weeks of treatment. ABX464 is rapidly metabolized to ABX464-N-Glu which had a much longer half-life compared to ABX464 (about 100 hours, data not shown).

		ABX464 50 mg			ABX464 100 mg		
Day		t_{max}* (h)	C_{max} (ng/mL)	AUC_{0-t} (h*ng/mL)	t_{max}* (h)	C_{max} (ng/mL)	AUC_{0-t} (h*ng/mL)
0	N	20	20	20	18	18	17
	Mean	2.00	35.9	53.05	3.00	69.0	90.94
	SD	0.57	36.7	55.34	0.60	72.7	71.56
	CV%	1.08-3.00	102.2	104.3	1.00-3.00	105.3	78.7
	GM	2.27	18.7	24.40	2.50	49.4	71.46
14	N	20	20	19	14	14	14
	Mean	2.00	16.9	28.49	2.50	19.4	35.20
	SD	0.73	12.5	21.41	0.83	20.7	44.48
	CV%	0.00-3.10	73.9	75.1	1.00-3.00	106.3	126.4
	GM	NC	11.9	21.89	2.10	11.8	17.97
56	N	17	17	17	8	8	8
	Mean	2.00	25.5	37.51	3.00	34.9	48.11
	SD	0.75	30.2	51.32	0.51	25.5	36.34
	CV%	1.00-3.08	118.4	136.8	2.00-3.00	73.1	75.5
	GM	1.92	12.5	15.57	2.58	21.2	26.99

* Median and Min-Max are presented instead of Mean and CV% ; NC: Not calculable since at least one value equal to zero

Concentrations in plasma samples were determined using protein precipitation followed by liquid chromatography coupled to a tandem mass spectrometry (LC/MS/MS) method with a limit of quantification (LOQ) of 0.500 ng/mL for ABX464.