Supplementary information

Notes on Figure 2

The response curves shown in Figure 1 (in the main article) were examined to determine a suitable form for parameterization of the time function in the statistical model: i.e., the method employed to model the shapes of the curves. It was concluded that each curve could be well approximated by 3 linear pieces: from day 1 to day 28, from day 29 to day 56, and from day 57 to day 84.

On the COAT scale for the knee joint, the differences between treatments on the 3 slope segments were as follows: there was a non-significant greater rate of reduction in placebo than active between day 1 and day 28 (0.0145 difference per day, p=0.176); there was a non-significant smaller rate of reduction in placebo than active between day 29 and day 56 (0.00062 difference per day, p=0.494); and there was an increase in placebo and a decrease in active between day 57 and day 84 with this difference being non-significant (0.0042 difference per day, p=0.397). Mean COAT scale scores for the knee joint reduced from 3.19 at day 1 to 2.21 at day 84 (30.6%) in the placebo group and from 3.03 at day 1 to 2.15 at day 84 (29.0%) in the active group. The overall difference (day 1 today 84) in response slopes between placebo and active for the knee joint was non-significant with an estimate = 0.00118 per day, SE=0.00577, and p=0.838. In addition, there were no significant (p<0.05) differences between treatments on COAT scale mean scores for the knee joint at any of day 1, day 28, day 56, or day 84.

On the COAT scale for the hip joint, the differences between treatments on the 3 slope segments (Treatment * F1, Treatment * F2, Treatment * F3) were as follows: there was a non-significantly smaller rate of reduction in placebo than active between day 1 and day 28 (0.0150 difference per day, p=0.307); there was a reduction in placebo and an increase in active between day 29 and day 56 with this difference being non-significant (0.0239 difference per day, p=0.057); and there was a non-significantly greater rate of increase in placebo than active between day 57 and day 84 (0.0076 difference per day, p=0.609). Mean COAT scores for the hip joint reduced from 3.37 at day 1 to 2.49 at day 84 (26.3%) in placebo and from 4.10 at day 1 to 3.26 at day 84 (20.3%) in active. The overall difference (day 1 to day 84) in response slopes between placebo and active for the hip joint was non-significant with an estimate = 0.00062 per day, SE=0.00798 and p=0.938. In addition, there were no significant (p<0.05) differences between treatments on COAT scale mean scores for the hip joint at any of day 1, day 28, day 56, or day 84.

Statistical data

Table S1 reports the removal sequence of the fixed effects and results of tests of their significance prior to their removal, and tests of the significance of effects retained in the final model. The 3 linear functions of day (F1, F2, and F3) were treated as a set, to be either removed or retained together.

Tables S2-S12 provide the descriptive statistics and outcomes for the other aspects of the study discussed in the results section of the main paper.

Table S1. Removal sequence of fixed effects, results of tests of their significance prior to their removal, and tests of significance for effects retained in final model

	Removal	Test of significance at removal		
Effect	sequence	DF^2	F	P
Intercept[1]	Retained	129.705	299.793	0.000

Treatment	*5*	*92.979*	*0.590*	*0.444*
Joint	*6*	*93.988*	*2.056*	*0.155*
F1	Retained	854.539	47.597	0.000
F2	Retained	727.676	4.180	0.041
F3	Retained	854.000	.802	0.371
*Treatment * Joint*	*3*	*92.013*	*0.721*	*0.398*
*Treatment * F1*	*2*	*848.948*	*0.239*	*0.625*
*Treatment * F2*	*2*	*722.997*	*0.334*	*0.563*
*Treatment * F3*	*2*	*849.412*	*0.406*	*0.524*
*Joint * F1*	*4*	*854.667*	*3.047*	*0.081*
*Joint * F2*	*4*	*727.609*	*2.006*	*0.157*
*Joint * F3*	*4*	*854.224*	*0.560*	*0.455*
*Treatment * Joint * F1*	*1*	*848.812*	*2.637*	*0.105*
*Treatment * Joint * F2*	*1*	*722.434*	*3.785*	*0.052*
*Treatment * Joint * F3*	*1*	*850.188*	*0.035*	*0.852*

1. In the final model, the intercept is the mean COAT score at day 1; 2. Denominator degrees of freedom. Numerator degrees of freedom = 1 for all effects.

Table S2. Descriptive statistics (mean, median, sd, minima, maxima) for % compliance by treatment and time together with results of t-tests

	Placebo (n=42)					Active(n=54)					t-test
Period	Mean	Median	SD	Min	Max	Mean	Median	SD	Min	Max	P value
Baseline to week 4	95.0	98.0	7.31	73	100	96.3	100.0	5.18	82	100	0.297
Week 4 to week 8	94.0	96.0	7.03	75	100	94.4	96.0	7.50	63	100	0.772
Week 8 to week 12	91.0	93.0	8.25	73	100	93.1	95.5	8.48	60	100	0.210

Table S3. Estimated means over time for % compliance from repeated measures analysis of variance.

Period	Mean	SE	95% CI	
Baseline to week 4	95.646	0.638	94.4	96.9
Week 4 to week 8	94.171	0.750	92.7	95.7
Week 8 to week 12	92.041	0.862	90.3	93.8

Table S4. Secondary outcomes CRP, IL-6, log(IL), TNF-alpha (means, SD, minima and maxima) by treatment at baseline and completion (week 12).

Secondar	Occasion		Placebo			Active	

y Outcomes		N	Mean	SD	Min	Max	N	Mean	SD	Min	Max
CRP	Baseline	42	0.41	0.462	0.0	2.4	54	0.49	0.673	0.0	3.3
	Completion	42	0.30	0.358	0.0	2.0	54	0.56	1.052	0.0	6.6
IL-6	Baseline	42	2.15	1.786	0.5	8.0	54	1.75	1.048	0.5	4.7
	Completion	42	1.66	1.048	0.4	4.5	54	2.06	1.533	0.4	10.5
log(IL-6)	Baseline	42	0.22	0.30	-0.29	0.91	54	0.17	0.25	-0.29	0.67
	Completion	42	0.14	0.26	-0.40	0.65	54	0.20	0.25	-0.40	1.02
TNF-alpha	Baseline	42	1.55	0.771	0.7	5.2	54	1.54	0.797	0.4	4.8
	Completion	42	1.67	0.936	0.6	5.2	54	1.79	1.001	0.4	5.4

The results of independent t-tests for the secondary outcome measures showed no difference between treatments (p>0.05) for any of the outcomes at baseline.

Table S5. Secondary outcomes: Results of repeated measures ANOVA

	p-values for Repeated Measures		
	Time	Treatment by time	Treatment
CRP	0.779	0.108	0.218
IL-6	0.485	0.004	0.995
log(IL-6)	0.794	0.004	0.749
TNF alpha	0.016	0.392	0.749

Table S6. BMI (means, median, SD, minima and maxima) by treatment at baseline, week 4, week 8 and completion (week 12).

	Placebo						Active					
	N	Mean	Median	SD	Min	Max	N	Mean	Median	SD	Min	Max
Baseline	42	28.8	28.1	5.3	19.7	48.4	54	28.7	27.8	4.6	18.3	39.3
Week 4	40	29.3	28.6	5.1	21.2	48.4	50	29.0	27.9	4.5	22.7	38.6
Week 8	39	29.1	28.4	4.9	20.9	47.3	53	28.9	28.0	4.6	18.1	39.3
Week 12	39	29.3	29.0	5.2	19.7	47.3	53	28.7	27.9	4.5	17.9	38.6

Table S7. Estimated means for time and treatment by time effects from multilevel AR1 model for BMI.

	Time		Placebo		Active	
Time	Mean	SE	Mean	SE	Mean	SE
Baseline	28.72	0.50	28.79	0.75	28.66	0.66
Week 4	28.95	0.50	29.09	0.75	28.81	0.66

Week 8	28.96	0.50	29.16	0.75	28.77	0.66
Week 12	28.91	0.50	29.19	0.75	28.64	0.66

Table S8. Results of post hoc comparisons of baseline compared to week 4, 8, 12 for BMI for the significant time and treatment by time interaction

		For time effect			For Treatment by time interaction					
					Placebo			Active		
Post hoc comparison		Mean diff	SE	P value	Mean diff	SE	P value	Mean diff	SE	P value
Baseline vs	Week 4	-0.226	0.060	0.001	-0.301	0.090	0.005	-0.152	0.079	0.339
	Week 8	-0.242	0.069	0.004	-0.368	0.105	0.003	-0.115	0.090	1.000
	Week 12	-0.188	0.073	0.065	-0.399*	0.110	0.002	0.024	0.094	1.000

Table S9. Blood Safety (means, SD, minima and maxima) by treatment and measurement occasion.

	Placebo					Active				
	N	Mean	SD	Min	Max	N	Mean	SD	Min	Max
Haemotology Baseline										
Red Cell Count	42	4.60	0.60	4.0	6.0	54	4.49	0.51	4.0	6.0
Haemoglobin	42	145.21	13.68	119	176	54	142.35	10.32	126	167
Haemacrit	42	0.05	0.15	0.00	0.52	54	0.08	0.16	0.00	0.45
Mean Corpuscular Volume	42	92.10	3.75	86	101	54	91.67	4.08	76	99
White Cell Count	42	6.25	1.87	3.9	12.0	54	5.91	1.25	3.3	10.0
Lymphocytes	42	2.03	0.75	1	4	54	1.92	0.55	1	4
Monocytes	42	0.35	0.48	0.0	1.4	54	0.25	0.38	0.0	1.0
Neutrophils	42	3.41	1.42	1.8	7.0	54	3.27	0.93	1.6	6.0
Basophils	42	0.00	0.00	0.0	0.0	53	0.00	0.01	0.0	0.1
Eosinophils	42	0.06	0.22	0.0	1.0	54	0.07	0.21	.00	1.0
Platelets	42	225.50	53.48	108	349	53	232.34	44.29	127	356
Biochemistry Baseline										
Alkaline Phosphatase	42	74.21	28.47	20	166	54	71.74	16.70	46	128
Serum Alanine	42	23.67	16.81	6	91	54	22.0	7.50	7	47

Aminotransferase							4			
Aspartate Aminotransferase	36	21.78	9.06	5	63	44	21.16	4.20	13	31
Gamma Glutamyl Transferase	42	30.33	24.84	10	144	54	32.20	23.81	9	126
Bilirubin	42	13.12	5.64	6	34	54	10.87	5.08	1	34
Protein	42	72.93	4.36	64	81	54	71.69	4.17	61	86
Albumin	42	40.02	3.35	32	46	54	40.00	3.68	33	50
Sodium	42	139.26	1.91	134	143	54	138.94	1.95	132	142
Potassium	42	4.40	0.85	0	5	54	4.50	0.48	4	5
Chloride	42	104.14	1.87	100	108	54	104.22	2.65	94	110
Bun/Urea	42	5.97	1.49	3	9	54	5.51	1.31	2	9
Creatine	42	74.90	13.18	56	109	54	72.28	15.10	53	117
Haemotology at Completion										
Red Cell Count	42	4.38	0.49	3.9	5.0	54	4.34	0.51	3.6	6.0
Haemoglobin	42	140.17	11.01	118	160	54	138.65	9.96	110	169
Haemacrit	42	0.05	0.14	.00	.47	54	0.07	0.15	.00	.41
Mean Corpuscular Volume	42	91.79	3.59	86	101	54	91.17	4.19	75	98
White Cell Count	42	6.20	1.66	3.4	11.0	54	6.07	1.21	3.4	9.0
Lymphocytes	42	2.15	0.58	1	4	54	1.95	0.58	1	4
Monocytes	42	0.42	0.48	0.0	1.0	54	0.46	0.46	0.0	1.0
Neutrophils	42	3.34	1.33	1.4	8.0	54	3.29	1.00	1.8	6.6
Basophils	42	0.00	0.00	.0	.0	54	0.00	0.01	.0	.1
Eosinophils	42	0.06	0.22	0.0	1.0	54	0.11	0.27	0.0	1.0
Platelets	42	217.76	48.61	142	328	54	223.57	45.19	74	321
Biochemistry at Completion										
Serum Alanine Aminotransferase	42	21.24	10.72	8	53	54	22.63	7.56	6	42
Aspartate Aminotransferase	37	19.97	6.76	0	35	43	21.58	6.90	4	37
Gamma Glutamyl Transferase	42	28.90	21.34	10	125	54	32.35	27.12	10	142

Bilirubin	42	11.40	3.67	6	21	54	10.19	4.28	4	29
Protein	42	71.62	3.57	65	79	54	70.80	3.75	59	78
Albumin	42	40.79	2.70	35	47	54	40.78	2.99	35	49
Sodium	42	139.31	1.84	135	143	54	139.63	2.33	129	143
Potassium	42	4.25	0.43	4	5	54	4.21	0.48	3	6
Chloride	42	105.52	2.32	101	112	54	105.63	2.66	97	110
Bun/Urea	42	5.83	1.21	4	9	54	5.84	1.62	3	10
Creatine	42	75.33	13.63	58	112	54	73.57	14.58	57	124

Table S10. Results of repeated measurement analysis for hematology and biochemical blood measures

	p values for Repeated Measures		
	Time	Treatment by time	Treatment
Haemotology			
Red Cell Count	0.000	0.338	0.430
Haemoglobin	0.000	0.280	0.326
Haemacrit	0.001	0.789	0.441
Mean Corpuscular Volume	0.001	0.423	0.515
White Cell Count	0.626	0.381	0.409
Lymphocytes	0.180	0.412	0.193
Monocytes	0.002	0.127	0.755
Neutrophils	0.787	0.662	0.642
Basophils	1.000	1.000	0.207
Eosinophils	0.408	0.408	0.416
Platelets	0.000	0.819	0.511
Biochemistry			
Alkaline Phosphatase	0.003	0.162	0.906
Serum Alanine Aminotransferase	0.349	0.125	0.953
Aspartate Aminotransferase	0.641	0.330	0.867
Gamma Glutamyl Transferase	0.621	0.543	0.587
Bilirubin	0.004	0.214	0.052
Protein	0.001	0.510	0.174
Albumin	0.000	0.696	0.980
Sodium	0.041	0.075	0.997
Potassium	0.006	0.382	0.697
Chloride	0.000	0.949	0.839

Bun/Urea	0.489	0.075	0.387
Creatine	0.141	0.457	0.447

Table S11. Numbers and percentages of adverse events experienced by treatment group between weeks 0-4, 4-8 and 8-12, and over the full 12 weeks

	Placebo		**Active**		
	Number	Percent	Number	Percent	P value
Week 0-4	3	7.3	2	3.9	0.653
Week 4-8	1	2.4	1	1.9	1.00
Week 8-12	1	2.4	0	0.0	0.437
Overall	5	11.9	3	5.6	0.292