SUPPLEMENTARY MATERIAL

Appendix S1: Additional inclusion criteria

Patients were included if they also met any of the following criteria:

- Had not received methotrexate (MTX) for at least 4 weeks before and including the baseline visit or had been taking MTX for at least 12 weeks immediately before and including the baseline visit and were on a stable dose of 10 to 20 mg/m^2 for at least 8 weeks before and including the baseline visit, together with either folic acid or folinic acid

- Had not received oral glucocorticoids at the baseline visit or had been taking oral glucocorticoids at a stable dose for at least 4 weeks before and including the baseline visit (no greater than 10 mg/day or 0.2 mg/kg/day)

- Were not taking non-steroidal anti-inflammatory drugs (NSAIDs) at baseline or were not taking more than one type of NSAID at a stable dose (less than or equal to the recommended daily dose) for at least 2 weeks before and including the baseline visit

- Had never been treated with biologics or had been previously treated with biologics and discontinued them for at least the following periods: anakinra, 1 week; etanercept, 2 weeks; rilonacept, 5 weeks; infliximab or adalimumab, 8 weeks; abatacept,12 weeks; canakinumab, 20 weeks, before and including the baseline visit

- Were females of childbearing potential and were using a reliable means of contraception throughout the study and up to 12 weeks after the last infusion of study drug

Appendix S2: Robustness of the primary end point analysis

The robustness of the results of the statistical procedure used for the primary end point analysis was assessed by logistic regression analysis of the proportion of patients with juvenile idiopathic arthritis–flare in the intent-to-treat population during part 2. This analysis showed a statistically significant treatment difference in favour of tocilizumab (odds ratio, 0.35; 95% confidence interval: 0.17, 0.71; p=0.0035) and, hence, was consistent with the primary analysis.

Supplementary Table S1 Overview of hierarchical analysis of significance testing at week 40 (ITT)

	End point	All placebo N=81	All tocilizumab[a] N=82	Difference[a] tocilizumab vs placebo (95% CI)	p
Primary end point					
1	Proportion with JIA-ACR30 flare (compared with week 16), n (%)	39 (48.1)	21 (25.6)	–0.21 (–0.35, 0.08)	0.0024
Secondary end points					
2	Proportion of patients with JIA-ACR30 improvement, n (%)	44 (54.3)	61 (74.4)	0.09 (0.05, 0.33)	0.0084
3	Proportion of patients with JIA-ACR50 improvement, n (%)	42 (51.9)	60 (73.2)	0.20 (0.06, 0.34)	0.0050
4	Proportion of patients with JIA-ACR70 improvement, n (%)	34 (42.0)	53 (64.6)	0.22 (0.07, 0.37)	0.0032
5	Change from baseline in number of active joints, adjusted mean	−11.4	−14.3	–2.9 (–5.7, –0.1)	0.0435
6	Change from baseline in physician global assessment VAS, adjusted mean	−35.2	−45.2	–9.9 (–16.5, –3.4)	0.0031
7	Change from baseline in the pain VAS, adjusted mean	−22.3	−32.4	–10.2 (–17.6, –2.7)	0.0076
8	Change from baseline in number of joints with LOM, adjusted mean	−7.7	−9.5	–1.8 (–4.1, 0.5)	0.1229
9	Change from baseline in patient global assessment of well-being adjusted mean	−24.7	−32.1	–7.4 (–14.8, 0.0)	[b]
10	Change from baseline in ESR (mm/h), adjusted mean	−12.0	−26.3	–14.3 (–19.6, –9.0)	[b]

11	CHAQ-DI score	–0.6	–0.8	–0.2 (–0.4, 0.0)	[b]
12	Proportion with JIA-ACR90 improvement, n (%)	19 (23.5)	37 (45.1)	0.21 (0.07, 0.35)	[b]
13	Proportion with inactive disease, n (%)	14 (17.3)	30 (36.6)	0.18 (0.05, 0.32)	[b]

CHAQ-DI, Childhood Health Assessment Questionnaire–Disability Index; CI, confidence interval; ESR; erythrocyte sedimentation rate; ITT, intent-to-treat; JIA-ACR, juvenile idiopathic arthritis–American College of Rheumatology; LOM, limitation of movement; VAS, Visual Analogue Scale (0-100 mm).

[a]Adjusted for baseline stratification factors (background use of methotrexate and oral glucocorticoids).

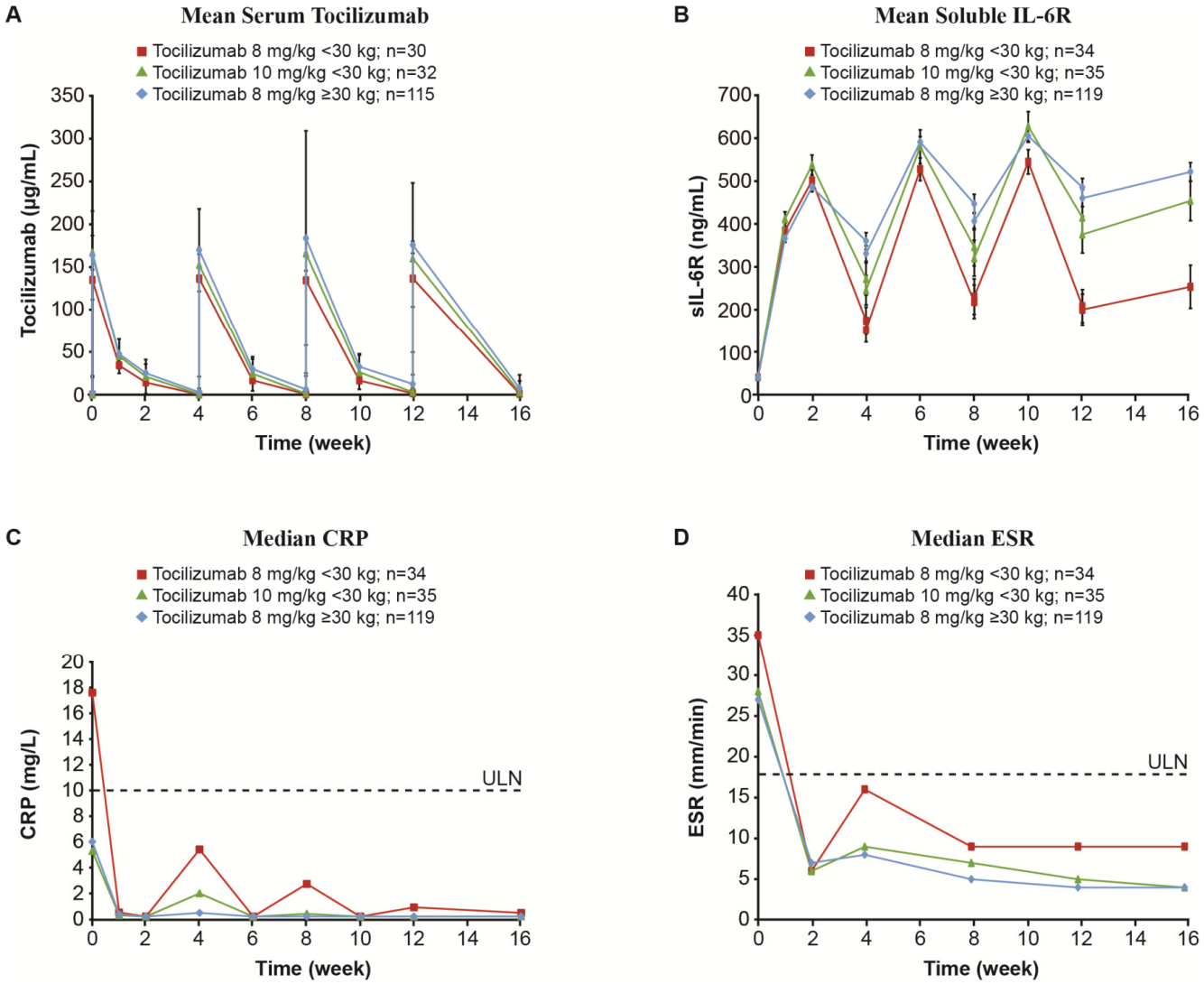
[b]p values were not provided because they fell below a non-significant parameter in the hierarchical chain to address multiplicity. The hierarchical chain of assessment for secondary end points for the study was broken at the assessment of number of joints with LOM; hence, treatment significance was not reported below that point in the chain of assessment.

Supplementary Table S2 Summary of observed tocilizumab pre-dose trough concentration (C_{min}) at week 16 (steady state) by treatment group

Pharmacokinetic parameters (mean ± SD)	**Tocilizumab 8 mg/kg <30 kg**	**Tocilizumab 10 mg/kg <30 kg**	**Tocilizumab 8 mg/kg ≥30 kg**
Observed	n = 27	n = 29	n = 113
C_{week16}, µg/mL	0.98 ± 2.26	2.75 ± 4.19	7.44 ± 8.48

C_{week16}, observed predose concentration at week 16; SD, standard deviation.
All patients with at least one quantifiable tocilizumab serum concentration were included in the pharmacokinetic analysis.

Supplementary Figure S1 (A) Mean serum tocilizumab concentration in part 1. (B) Mean soluble IL-6R concentration in part 1. (C) Median CRP concentration in part 1. (D) Median ESR concentration in part 1. Error bars represent (A) standard deviation and (B) standard error of the mean. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL-6R, interleukin-6 receptor; ULN, upper limit of normal.


A
Mean Serum Tocilizumab
Tocilizumab 8 mg/kg <30 kg; n=30
Tocilizumab 10 mg/kg <30 kg; n=32
Tocilizumab 8 mg/kg ≥30 kg; n=115
Tocilizumab (µg/mL)
Time (week)
B
Mean Soluble IL-6R
Tocilizumab 8 mg/kg <30 kg; n=34
Tocilizumab 10 mg/kg <30 kg; n=35
Tocilizumab 8 mg/kg ≥30 kg; n=119
sIL-6R (ng/mL)
Time (week)
C
Median CRP
Tocilizumab 8 mg/kg <30 kg; n=34
Tocilizumab 10 mg/kg <30 kg; n=35
Tocilizumab 8 mg/kg ≥30 kg; n=119
CRP (mg/L)
ULN
Time (week)
D
Median ESR
Tocilizumab 8 mg/kg <30 kg; n=34
Tocilizumab 10 mg/kg <30 kg; n=35
Tocilizumab 8 mg/kg ≥30 kg; n=119
ESR (mm/min)
ULN
Time (week)