Clinical trial results:
Randomised Control Trial of the Clinical Effectiveness, Safety and Cost Effectiveness of Adalimumab in Combination with Methotrexate for the Treatment of Juvenile Idiopathic Arthritis Associated Uveitis.

Summary

EudraCT number	2010-021141-41
Trial protocol	GB
Global end of trial date	14 December 2016
Results information	
Result version number	v2 (current)
This version publication date	04 May 2019
First version publication date	23 March 2018
Version creation reason	• Changes to summary attachments During site closedown for the trial, data were identified for participants that had not been sent to CTRC by sites and subsequently were not present in the database at the time of data lock. The impact was assessed by the statistics team who confirmed the omitted data would have minimal impact on the trial results so therefore the database was not unlocked. This event was not considered a serious breach. Full details are described within the attached file note. The report has not changed.
Summary attachment (see zip file)	Baseline Data (Ocular Baseline Data.pdf) Supplementary Material - Open Label Phase Results (EudraCT Supplementary Material - Open-label phase.pdf) File note (SYCAMORE File note - Data received following database lock.pdf)

Trial information

Trial identification	
Sponsor protocol code	CH/2008/3061
Additional study identifiers	
ISRCTN number	ISRCTN10065623
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Funding reference numbers: HTA 90/51/01; ARUK 19612

Notes:

Sponsors	
Sponsor organisation name	University Hospitals Bristol NHS Foundation Trust
Sponsor organisation address	UH Bristol Education Centre, Level 3, Upper Maudlin Street, Bristol, United Kingdom, BS2 8AE
Public contact	Ashley Jones, Clinical Trials Research Centre, University of

	Liverpool, +44 151 795 8751, ctrcqa@liverpool.ac.uk
Scientific contact	Ashley Jones, Clinical Trials Research Centre, University of Liverpool, +44 151 795 8751, ctrcqa@liverpool.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000366-PIP12-02
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 August 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 June 2015
Global end of trial reached?	Yes
Global end of trial date	14 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare how effective the use of adalimumab, in combination with methotrexate versus methotrexate alone with regard to controlling disease activity in refractory uveitis associated with juvenile idiopathic arthritis.

Please note: As stated in the protocol, the formal end of trial is defined as the date of final database lock which was on 02/08/17.

Protection of trial subjects:

The first dose of IMP was administered by the research / clinical team looking after the patient. All participants or a family member were invited to self-administer the study treatment after the first dose and taught as such to do this under procedures in place within each participating centre for teaching this. The first dose they administered was also be under supervision of the clinical team, who ensured they are confident and able to carry out all parts of the procedure appropriately and accurately. This would allow patients to then have their remaining trial treatment in the familiar surroundings of their home to reduce distress. If they did not want to do this, then arrangements were put in place on an individual basis for ensuring trial medication is administered as prescribed.

Study visits and study assessments were set around routine clinical care to minimise the inconvenience for patients and families, travel expenses were provided for visits outside of routine care that were specific for SYCAMORE.

Background therapy:

All subjects to receive a stable dose of methotrexate

Evidence for comparator:

Methotrexate (MTX) is well established as the first-line disease modifying agent in the management of JIA. MTX is also thought to be effective for JIA-associated uveitis in children with moderate-to-severe uveitis, but there have been no prospective randomised placebo-controlled trials of MTX or steroid

regimens in JIA-associated uveitis.

Adalimumab is a fully human monoclonal antibody engineered by gene technology that uses site-directed mutagenesis to enhance its binding efficiency to tumor necrosis factor (TNF). It does not contain nonhuman or artificial protein sequences. There are no prospective studies of efficacy and safety of anti-TNF agents in JIA-associated uveitis. In the randomised controlled trial of adalimumab in JIA that demonstrated safety and efficacy, the most commonly reported adverse events were infections and injection-site reactions. Serious adverse events considered possibly related to study drug by the investigator occurred in 14 patients.

Actual start date of recruitment	21 October 2011
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	United Kingdom: 90
Worldwide total number of subjects	90
EEA total number of subjects	90

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)	69
Adolescents (12-17 years)	21
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial took place in 17 United Kingdom centres; 14 of these centres randomised at least one participant. The first patient was randomised on the 27th October 2011 and the last patient was randomised on the 31st March 2015.

Pre-assignment

Screening details:

There was a total of 332 patients assessed for eligibility from 519 screenings (patients could be screened on multiple occasions). 130 (39%) were eligible and 90 were consented and were randomised.

Pre-assignment period milestones

Number of subjects started	90
Number of subjects completed	90

Period 1

Period 1 title	Blinded Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

This trial was placebo-controlled and all study assessments were carried out by health professionals, parents/carers and patients without knowledge of treatment allocation. The placebo solution for the injection was a clear, colourless solution presented in a single-use vial for the injection in volumes of 0.8mL.

The packaging of the kit of adalimumab and placebo were identical. Each kit consisted of two vials of adalimumab or placebo in an outer carton.

Arms

Are arms mutually exclusive?	Yes
Arm title	Adalimumab (blinded phase)

Arm description:

Adalimumab subcutaneous injection every 2 weeks for 18 months.

Participants in the adalimumab group who were still on treatment at the point of the TSC decision to unblind subsequently took part in an open-label phase of the trial. Placebo participants moved straight to follow-up. See attached summary for the results of any analyses including the open-label phase data.

Arm type	Experimental
Investigational medicinal product name	Adalimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

20mg for participants weighing <30kg; 40mg for participants weighing ≥ 30kg

Arm title	Placebo (blinded phase)

Arm description:

Placebo subcutaneous injection every 2 weeks for 18 months

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo subcutaneous injection every 2 weeks for 18 months

Number of subjects in period 1	Adalimumab (blinded phase)	Placebo (blinded phase)
Started	60	30
Completed	58	29
Not completed	2	1
Consent withdrawn by subject	2	1

Period 2

Period 2 title	Follow-up
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Adalimumab (follow-up)

Arm description:

The original trial design included an 18 month treatment period followed by an 18 month follow-up period. If the patient was deemed to be classified as a treatment failure or discontinued their allocated treatment (either before or at 18 months) they were to enter into the follow-up period of the trial. During this follow-up period, patients were to be assessed at 3, 6, 9, 12, 15 and 18 months post treatment cessation.

A later change to the study protocol (see More Information: Substantial Protocol Amendments section) allowed the follow-up period to be reduced from 18 months to 6 months. The assessments were then carried out at two follow-up visits at 3 months and 6 months post treatment cessation.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Placebo (follow-up)

Arm description:

See above.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Adalimumab (follow-up)	Placebo (follow-up)
Started	58	29
Completed	58	29

Baseline characteristics

Reporting groups	
Reporting group title	Adalimumab (blinded phase)
Reporting group description:	
Adalimumab subcutaneous injection every 2 weeks for 18 months. Participants in the adalimumab group who were still on treatment at the point of the TSC decision to unblind subsequently took part in an open-label phase of the trial. Placebo participants moved straight to follow-up. See attached summary for the results of any analyses including the open-label phase data.	
Reporting group title	Placebo (blinded phase)
Reporting group description:	
Placebo subcutaneous injection every 2 weeks for 18 months	

Reporting group values	Adalimumab (blinded phase)	Placebo (blinded phase)	Total
Number of subjects	60	30	90
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)	46	23	69
Adolescents (12-17 years)	14	7	21
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Age at randomisation			
Units: years			
arithmetic mean	9.07	8.56	
standard deviation	± 3.94	± 3.79	-
Gender categorical			
Gender			
Units: Subjects			
Female	47	23	70
Male	13	7	20
Number of study eyes Units: Subjects			
Unilateral	43	22	65
Bilateral	17	8	25
Weight (kg) Units: Subjects			
<30kg	33	17	50
>=30kg	26	13	39
Unobtainable	1	0	1
Type of JIA (Internation League of Associations for Rheumatology (ILAR) classification)			

Units: Subjects			
Extended oligoarthritis	14	7	21
Persistent oligoarthritis	36	17	53
Polyarthritis RF negative	8	4	12
Polyarthritis RF positive	1	1	2
Psoriatic arthritis	1	1	2
Anti-nuclear antibody Units: Subjects			
Negative	24	10	34
Positive	33	15	48
Not carried out	3	5	8
Double-stranded deoxyribonucleic acid Units: Subjects			
Negative	47	22	69
Positive	3	2	5
Not carried out	10	6	16
Rheumatoid factor Units: Subjects			
Negative	46	20	66
Positive	1	3	4
Not carried out	13	7	20
Disease duration			
6 adalimumab and 4 placebo participants had unobtainable disease duration.			
Units: years			
arithmetic mean	5.58	4.81	
standard deviation	± 3.69	± 3.19	-
Physician global assessment of disease activity			
2 adalimumab and 1 placebo participants had unobtainable physician global assessment of disease activity.			
Units: Physician global assessment			
arithmetic mean	0.76	0.83	
standard deviation	± 1.48	± 1.09	-
Active joint count [all joints] Units: Active joints			
arithmetic mean	0.57	1.1	
standard deviation	± 2.03	± 2.23	-
Swollen joint count [all joints] Units: Swollen joints			
arithmetic mean	0.55	1	
standard deviation	± 1.66	± 1.55	-

End points

End points reporting groups

Reporting group title	Adalimumab (blinded phase)

Reporting group description:

Adalimumab subcutaneous injection every 2 weeks for 18 months.

Participants in the adalimumab group who were still on treatment at the point of the TSC decision to unblind subsequently took part in an open-label phase of the trial. Placebo participants moved straight to follow-up. See attached summary for the results of any analyses including the open-label phase data.

Reporting group title	Placebo (blinded phase)

Reporting group description:

Placebo subcutaneous injection every 2 weeks for 18 months

Reporting group title	Adalimumab (follow-up)

Reporting group description:

The original trial design included an 18 month treatment period followed by an 18 month follow-up period. If the patient was deemed to be classified as a treatment failure or discontinued their allocated treatment (either before or at 18 months) they were to enter into the follow-up period of the trial. During this follow-up period, patients were to be assessed at 3, 6, 9, 12, 15 and 18 months post treatment cessation.

A later change to the study protocol (see More Information: Substantial Protocol Amendments section) allowed the follow-up period to be reduced from 18 months to 6 months. The assessments were then carried out at two follow-up visits at 3 months and 6 months post treatment cessation.

Reporting group title	Placebo (follow-up)

Reporting group description:

See above.

Primary: Blinded Phase: Time to treatment failure

End point title	Blinded Phase: Time to treatment failure

End point description:

Treatment failure was classified as occurrence of one of the following:

1) Anterior segment inflammatory score grade (SUN criteria) following at least 3 months of therapy.
2) Use of Concomitant Medications: At any time, requirement to use concomitant medications in manner out with pre-defined acceptable criteria, or any of the concomitant medications not allowed.
3) Intermittent or continuous suspension of study treatment (adalimumab/placebo) for a cumulative period longer than 4 weeks

Full details on the treatment failure criteria can be found within the protocol.

End point type	Primary

End point timeframe:

Participants were assessed for treatment failure from randomisation up until:
-time of treatment failure
-completion of 18 months of treatment
-unblinding following TSC decision,
whichever occurred first.

End point values	Adalimumab (blinded phase)	Placebo (blinded phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	30		
Units: Treatment Failures				
Failed treatment	14	17		
Censored	46	13		

Attachments (see zip file)	Blinded Phase - Primary Outcome.pdf

Statistical analyses

Statistical analysis title	Time to treatment failure
Comparison groups	Placebo (blinded phase) v Adalimumab (blinded phase)
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	0.51

Secondary: Blinded phase: Number of participants failing treatment

End point title	Blinded phase: Number of participants failing treatment

End point description:

Treatment failure was classified as occurrence of one of the following:
1) Anterior segment inflammatory score grade (SUN criteria) following at least 3 months of therapy.
2) Use of Concomitant Medications: At any time, requirement to use concomitant medications in manner out with pre-defined acceptable criteria, or any of the concomitant medications not allowed.
3) Intermittent or continuous suspension of study treatment (adalimumab/placebo) for a cumulative period longer than 4 weeks
Full details on the treatment failure criteria can be found within the protocol.

End point type	Secondary

End point timeframe:

Participants were assessed for treatment failure from randomisation up until:

-time of treatment failure
-completion of 18 months of treatment
-unblinding following TSC decision,

whichever occurred first.

End point values	Adalimumab (blinded phase)	Placebo (blinded phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	30		
Units: Treatment Failures				
Failed treatment	14	17		
Did not fail treatment	46	13		

Statistical analyses

Statistical analysis title	Number of participants failing treatment
Comparison groups	Placebo (blinded phase) v Adalimumab (blinded phase)
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	0.72

Secondary: Blinded phase: Total oral corticosteroid dose

End point title	Blinded phase: Total oral corticosteroid dose

End point description:

The total dose is calculated by summing the daily doses and standardised to per patient years.

End point type	Secondary

End point timeframe:

Participants are assessed from randomisation until:
-time of treatment failure
-completion of 18 months of treatment
-unblinding following TSC decision,
whichever occurred first.

End point values	Adalimumab (blinded phase)	Placebo (blinded phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[1]	1[2]		
Units: miligrams per patient year				
number (not applicable)				
Total dose per patient years	804.31	3767.74		

Notes:

[1] - 5 participants were taking oral corticosteroids at randomisation.

[2] - 1 participant was taking oral corticosteroids at randomisation.

Statistical analyses

Statistical analysis title	Total oral corticosteroid dose
Comparison groups	Adalimumab (blinded phase) v Placebo (blinded phase)
Number of subjects included in analysis	6
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Poisson regression
Parameter estimate	Rate ratio
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	0.23

Secondary: Blinded phase: Reduction in systemic corticosteroid dose from entry dose to 0mg

End point title	Blinded phase: Reduction in systemic corticosteroid dose from entry dose to 0mg

End point description:

Reduction in systemic corticosteroid dose from entry dose to 0mg will be analysed for a subset of patients, as not everyone will be taking systemic corticosteroids at randomisation.

The planned analysis was a competing risks time-to-event model. No comparative analysis was able to be performed due to the fact that statistical algorithm did not converge.

End point type	Secondary

End point timeframe:

Participants were assessed from randomisation up until:
-time of treatment failure
-completion of 18 months of treatment
-unblinding following TSC decision,
whichever occurred first.

End point values	Adalimumab (blinded phase)	Placebo (blinded phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[3]	1[4]		
Units: Events				
Reduced dose	3	1		
Censored	2	0		

Notes:

[3] - 5 participants were prescribed systemic corticosteroids >0mg at baseline.

[4] - 1 participant was prescribed systemic corticosteroids >0mg at baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Blinded phase: Rate of systemic corticosteroid dose from entry dose

End point title	Blinded phase: Rate of systemic corticosteroid dose from entry dose

End point description:

The total dose is calculated by summing the daily doses and standardised to per patient years.

End point type	Secondary

End point timeframe:

Participants were assessed from randomisation up until:
-time of treatment failure
-completion of 18 months of treatment
-unblinding following TSC decision,
whichever occurred first.

End point values	Adalimumab (blinded phase)	Placebo (blinded phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[5]	1[6]		
Units: miligrams per patient years				
number (not applicable)				
Total dose per patient years	804.31	3767.74		

Notes:

[5] - 5 participants were taking systemic corticosteroids at randomisation.

[6] - 1 participant was taking systemic corticosteroids at randomisation.

Statistical analyses

Statistical analysis title	Rate of systemic corticosteroids from entry dose
Comparison groups	Placebo (blinded phase) v Adalimumab (blinded phase)
Number of subjects included in analysis	6
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Poisson regression
Parameter estimate	Rate ratio
Point estimate	0.21

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	0.23

Secondary: Blinded phase: Time to reduction to <2 drops in topical corticosteroids

End point title	Blinded phase: Time to reduction to <2 drops in topical corticosteroids

End point description:

Time to reduction to < 2 drops for those patients already on >= 2 drops at randomisation.

End point type	Secondary

End point timeframe:

Participants were assessed from randomisation up until:
-time of treatment failure
-completion of 18 months of treatment
-unblinding following TSC decision,
whichever occurred first.

End point values	Adalimumab (blinded phase)	Placebo (blinded phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45[7]	18[8]		
Units: Events				
Reduced drops	24	3		
Censored	21	15		

Notes:

[7] - 45 participants were on ≥ 2 drops per day at baseline.

[8] - 18 participants were on ≥ 2 drops per day at baseline.

Statistical analyses

Statistical analysis title	Time to reduction to <2 drops

Statistical analysis description:

This was a competing risks analysis, accounting for the time to treatment failure.

Comparison groups	Placebo (blinded phase) v Adalimumab (blinded phase)
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	Fine and Gray
Parameter estimate	Hazard ratio (HR)
Point estimate	3.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.18
upper limit	25.2

Secondary: Blinded phase: Need for pulsed corticosteroid

End point title	Blinded phase: Need for pulsed corticosteroid
End point description: Need for pulsed corticosteroid.	
End point type	Secondary
End point timeframe: Participants were assessed from randomisation up until: -time of treatment failure -completion of 18 months of treatment -unblinding following TSC decision, whichever occurred first.	

End point values	Adalimumab (blinded phase)	Placebo (blinded phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	30		
Units: Events				
Needed pulsed corticosteroids	2	1		
Did not need pulsed corticosteroids	58	29		

Statistical analyses

Statistical analysis title	Need for pulsed corticosteroid
Comparison groups	Adalimumab (blinded phase) v Placebo (blinded phase)
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.99
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	10.59

Secondary: Blinded phase: Optic and Ocular: Number of participants with disease flares following a minimum of 3 months of disease control

End point title	Blinded phase: Optic and Ocular: Number of participants with disease flares following a minimum of 3 months of disease control

End point description:

Disease control is when a patient has a score of "0" for the field "AC cells (SUN)" for 3 months (12 weeks ± 7 days i.e. at least 11 weeks) from randomisation within each eligible eye and has had at least one topical treatment during this time.

Disease flares are defined as an increase in the "AC cells (SUN)" score at two consecutive visits at least 4 weeks apart.

Two analyses were performed for this outcome: 3 months disease control and a flare in at least one eye, and 3 months disease control in both eyes and a flare in at least one eye. The latter has been uploaded as a supplementary file.

End point type	Secondary

End point timeframe:

Participants were assessed from randomisation up until:
-time of treatment failure
-completion of 18 months of treatment
-unblinding following TSC decision,
whichever occurred first.

End point values	Adalimumab (blinded phase)	Placebo (blinded phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	30		
Units: Events				
Disease flare	5	1		
No disease flare	55	29		

Statistical analyses

Statistical analysis title	Disease flares following 3 months disease control
Comparison groups	Adalimumab (blinded phase) v Placebo (blinded phase)
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.66
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	20.45

Secondary: Blinded phase: Optic and Ocular: Number of participants with disease flares within the first 3 months of the study

End point title	Blinded phase: Optic and Ocular: Number of participants with disease flares within the first 3 months of the study

End point description:

Disease flare is defined by worsening based on SUN criteria.

Two analyses were due to be performed for this outcome: disease flare in at least one eye, and disease flare in both eyes. No participants who had a flare were eligible on both eyes and therefore the second analysis was not possible.

End point type	Secondary

End point timeframe:

Participants were assessed from randomisation up until:
-time of treatment failure
-completion of 18 months of treatment
-unblinding following TSC decision,
whichever occurred first.

End point values	Adalimumab (blinded phase)	Placebo (blinded phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	30		
Units: Events				
Disease flare	0	3		
No disease flare	60	27		

Statistical analyses

Statistical analysis title	Disease flare within first 3 months
Comparison groups	Adalimumab (blinded phase) v Placebo (blinded phase)
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.004
upper limit	1.36

Secondary: Blinded phase: Optic and Ocular: Visual acuity as measured by age-appropriate LogMAR assessment

End point title	Blinded phase: Optic and Ocular: Visual acuity as measured by age-appropriate LogMAR assessment

End point description:

Change in assessment over time.

Summary tables showing the number of assessments at each time point have been uploaded as a supplementary file.

End point type	Secondary

End point timeframe:

Participants were assessed from randomisation up until:
-time of treatment failure
-completion of 18 months of treatment
-unblinding following TSC decision,
whichever occurred first.

End point values	Adalimumab (blinded phase)	Placebo (blinded phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	30		
Units: LogMAR				
arithmetic mean (standard deviation)				
Best-case: Baseline	0.04 (± 0.15)	0.06 (± 0.12)		
Best-case: 1 month	0.03 (± 0.17)	0.02 (± 0.16)		
Best-case: 2 months	0.02 (± 0.17)	0.05 (± 0.18)		
Best-case: 3 months	0.00 (± 0.16)	0.01 (± 0.11)		
Best-case: 6 months	0.02 (± 0.20)	0.05 (± 0.16)		
Best-case: 9 months	-0.01 (± 0.14)	0.00 (± 0.17)		
Best-case: 12 months	-0.01 (± 0.14)	0.03 (± 0.14)		
Best-case: 15 months	0.00 (± 0.14)	0.00 (± 0.26)		
Best-case: 18 months	0.02 (± 0.13)	0.02 (± 0.21)		
Worst-case: Baseline	0.05 (± 0.16)	0.08 (± 0.12)		
Worst-case: 1 month	0.04 (± 0.18)	0.06 (± 0.17)		
Worst-case: 2 months	0.04 (± 0.19)	0.06 (± 0.18)		
Worst-case: 3 months	0.02 (± 0.20)	0.03 (± 0.12)		
Worst-case: 6 months	0.03 (± 0.20)	0.07 (± 0.19)		
Worst-case: 9 months	-0.01 (± 0.14)	0.04 (± 0.20)		
Worst-case: 12 months	0.00 (± 0.14)	0.08 (± 0.17)		
Worst-case: 15 months	0.00 (± 0.13)	0.00 (± 0.26)		
Worst-case: 18 months	0.04 (± 0.11)	0.02 (± 0.21)		

Attachments (see zip file)	Blinded Phase - LogMAR.pdf

Statistical analyses

Statistical analysis title	Joint Modelling for LogMAR (best-case)

Statistical analysis description:

Joint modelling of LogMAR estimating longitudinal treatment effects adjusted for dropout due to treatment failure.

In this analysis, when only one eye was involved the single LogMAR value was used. When there were two eyes involved, the best LogMAR measurement was used (the minimum of the 2 values).

Comparison groups	Adalimumab (blinded phase) v Placebo (blinded phase)

Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.51
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.02

Statistical analysis title	Joint Modelling for LogMAR (worst-case)

Statistical analysis description:

Joint modelling of LogMAR estimating longitudinal treatment effects adjusted for dropout due to treatment failure.

In this analysis, when only one eye was involved the single LogMAR value was used. When there were two eyes involved, the worst LogMAR measurement was used (the maximum of the 2 values).

Comparison groups	Adalimumab (blinded phase) v Placebo (blinded phase)
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.36
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.02

Secondary: Blinded phase: Optic and Ocular: Number of participants with resolution of associated optic nerve

End point title	Blinded phase: Optic and Ocular: Number of participants with resolution of associated optic nerve

End point description:

Assessed by slit lamp biomicroscopy or optical coherence tomography (OCT) where available.

Two analyses were due to be performed for this outcome: resolution in at least 1 eye, and resolution in both eyes. There were no participants who had associated optic nerve at baseline or developed this during the course of the study in the placebo group. It was, therefore, not possible to carry out either of the planned statistical tests of these data.

End point type	Secondary

End point timeframe:

Participants were assessed from randomisation up until:
-time of treatment failure
-completion of 18 months of treatment

-unblinding following TSC decision,
whichever occurred first.

End point values	Adalimumab (blinded phase)	Placebo (blinded phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[9]	0[10]		
Units: Events				
Resolved	2			
Not resolved	2			

Notes:

[9] - There were 4 participants who had associated optic nerve at baseline or developed it later.

[10] - There were 0 participants who had associated optic nerve at baseline or developed it later.

Statistical analyses

No statistical analyses for this end point

Secondary: Blinded phase: Optic and Ocular: Number of participants with resolution of macular oedema

End point title	Blinded phase: Optic and Ocular: Number of participants with resolution of macular oedema

End point description:

Assessed by slit lamp biomicroscopy or optical coherence tomography (OCT) where available.

Two analyses were performed for this outcome: resolution in at least 1 eye, and resolution in both eyes. The latter has been uploaded as a supplementary file.

End point type	Secondary

End point timeframe:

Participants were assessed for treatment failure from randomisation up until:
-time of treatment failure
-completion of 18 months of treatment
-unblinding following TSC decision,
whichever occurred first.

End point values	Adalimumab (blinded phase)	Placebo (blinded phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[11]	2[12]		
Units: Events				
Resolved	3	0		
Not resolved	1	2		

Notes:

[11] - There were 4 participants who had MO at baseline or developed it later.

[12] - There were 2 participants who had MO at baseline or developed it later.

Attachments (see zip file)	Blinded Phase - Macular Oedema.pdf

Statistical analyses

Statistical analysis title	Resolution of macular oedema
Comparison groups	Adalimumab (blinded phase) v Placebo (blinded phase)
Number of subjects included in analysis	6
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	74.52

Secondary: Blinded phase: Optic and Ocular: Number of participants with disease control for 3 months

End point title	Blinded phase: Optic and Ocular: Number of participants with disease control for 3 months

End point description:

Disease control is defined as zero cells, with topical treatment for 3 months.

Two analyses were performed for this outcome: disease control in at least 1 eye, and disease control in both eyes. The latter has been uploaded as a supplementary file.

End point type	Secondary

End point timeframe:

Participants were assessed for treatment failure from randomisation up until:
-time of treatment failure
-completion of 18 months of treatment
-unblinding following TSC decision,
whichever occurred first.

End point values	Adalimumab (blinded phase)	Placebo (blinded phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	30		
Units: Events				
Disease control	23	2		
No disease control	37	28		

Attachments (see zip file)	Blinded Phase - Number of participants with disease control for

Statistical analyses

Statistical analysis title	Disease control for 3 months
Comparison groups	Adalimumab (blinded phase) v Placebo (blinded phase)

Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	5.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.45
upper limit	22.78

Secondary: Blinded phase: Optic and Ocular: Number of participants with disease control for 6 months

End point title	Blinded phase: Optic and Ocular: Number of participants with disease control for 6 months

End point description:

Disease control is defined as zero cells, with topical treatment for 6 months.

Two analyses were performed for this outcome: disease control in at least 1 eye, and disease control in both eyes. The latter has been uploaded as a supplementary file.

End point type	Secondary

End point timeframe:

Participants were assessed for treatment failure from randomisation up until:
-time of treatment failure
-completion of 18 months of treatment
-unblinding following TSC decision,
whichever occurred first.

End point values	Adalimumab (blinded phase)	Placebo (blinded phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	30		
Units: Events				
Disease control	17	1		
No disease control	43	29		

Attachments (see zip file)	Blinded Phase - Number of participants with disease control for

Statistical analyses

Statistical analysis title	Disease control 6 months
Comparison groups	Adalimumab (blinded phase) v Placebo (blinded phase)

Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	8.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.19
upper limit	60.87

Secondary: Blinded phase: Optic and Ocular: Number of participants entering disease remission for 3 months

End point title	Blinded phase: Optic and Ocular: Number of participants entering disease remission for 3 months

End point description:

Disease remission is defined as zero cells without topical treatment for 3 months.

Two analyses were performed for this outcome: disease remission in at least 1 eye, and disease remission in both eyes. The latter has been uploaded as a supplementary file.

End point type	Secondary

End point timeframe:

Participants were assessed for treatment failure from randomisation up until:
-time of treatment failure
-completion of 18 months of treatment
-unblinding following TSC decision,
whichever occurred first.

End point values	Adalimumab (blinded phase)	Placebo (blinded phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	30		
Units: Events				
Remission	15	1		
No remission	45	29		

Statistical analyses

Statistical analysis title	Disease remission for 3 months
Comparison groups	Adalimumab (blinded phase) v Placebo (blinded phase)

Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	7.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.04
upper limit	54.12

Secondary: Blinded phase: Optic and Ocular: Number of participants entering disease remission for 6 months

End point title	Blinded phase: Optic and Ocular: Number of participants entering disease remission for 6 months

End point description:

Disease remission is defined as zero cells without topical treatment for 6 months.

Two analyses were performed for this outcome: disease remission in at least 1 eye, and disease remission in both eyes. The latter has been uploaded as a supplementary file.

End point type	Secondary

End point timeframe:

Participants were assessed for treatment failure from randomisation up until:
-time of treatment failure
-completion of 18 months of treatment
-unblinding following TSC decision,
whichever occurred first.

End point values	Adalimumab (blinded phase)	Placebo (blinded phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	30		
Units: Events				
Remission	13	0		
No remission	47	30		

Attachments (see zip file)	Blinded Phase - Number of participants with disease remission

Statistical analyses

Statistical analysis title	Disease remission 6 months
Comparison groups	Adalimumab (blinded phase) v Placebo (blinded phase)

Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	13.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	223.26

Secondary: Blinded phase: Optic and Ocular: Duration of sustaining inactive disease

End point title	Blinded phase: Optic and Ocular: Duration of sustaining inactive disease

End point description:

Inactive disease is defined as zero cells with or without topical treatment.

End point type	Secondary

End point timeframe:

Participants were assessed for treatment failure from randomisation up until:
-time of treatment failure
-completion of 18 months of treatment
-unblinding following TSC decision,
whichever occurred first.

End point values	Adalimumab (blinded phase)	Placebo (blinded phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	30		
Units: Days				
least squares mean (standard error)	180.91 (± 16.81)	16.36 (± 23.79)		

Statistical analyses

Statistical analysis title	Duration of inactive disease
Comparison groups	Adalimumab (blinded phase) v Placebo (blinded phase)
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	164.55

Confidence interval	
level	95 %
sides	2-sided
lower limit	104.41
upper limit	224.69

Secondary: Blinded phase: Quality of life assessments: Childhood Health Questionnaire (CHQ)

End point title	Blinded phase: Quality of life assessments: Childhood Health Questionnaire (CHQ)

End point description:

The CHQ consists of two scores:

Physical score (PhS)
Psychosocial score (PsS)

Summary tables showing the number of assessments at each time point have been uploaded as a supplementary file.

End point type	Secondary

End point timeframe:

Participants were assessed from randomisation up until:
-time of treatment failure
-completion of 18 months of treatment
-unblinding following TSC decision,
whichever occurred first.

End point values	Adalimumab (blinded phase)	Placebo (blinded phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53[13]	22[14]		
Units: CHQ				
arithmetic mean (standard deviation)				
PhS: Baseline	43.20 (± 11.84)	40.48 (± 16.36)		
PhS: 1 month	45.54 (± 11.29)	44.73 (± 12.10)		
PhS: 2 months	47.54 (± 10.69)	43.65 (± 15.56)		
PhS: 3 months	46.50 (± 13.13)	47.35 (± 7.97)		
PhS: 6 months	47.16 (± 11.84)	41.95 (± 15.79)		
PhS: 9 months	47.50 (± 11.26)	45.20 (± 14.77)		
PhS: 12 months	47.29 (± 13.06)	53.09 (± 4.79)		
PhS: 15 months	42.85 (± 15.88)	55.75 (± 2.48)		
PhS: 18 months	45.92 (± 12.06)	53.77 (± 9.71)		
PsS: Baseline	51.17 (± 9.53)	49.48 (± 7.55)		
PsS: 1 month	51.06 (± 10.36)	50.01 (± 10.27)		

PsS: 2 months	53.02 (± 10.00)	50.20 (± 10.75)		
PsS: 3 months	54.12 (± 9.02)	54.21 (± 8.57)		
PsS: 6 months	53.94 (± 9.79)	49.68 (± 11.56)		
PsS: 9 months	55.82 (± 6.84)	50.26 (± 13.72)		
PsS: 12 months	54.08 (± 9.22)	54.18 (± 8.83)		
PsS: 15 months	53.56 (± 7.76)	53.27 (± 11.83)		
PsS: 18 months	53.58 (± 11.71)	47.25 (± 18.64)		

Notes:

[13] - 53 had a baseline measurement.

[14] - 22 had a baseline assessment.

Attachments (see zip file)	Blinded Phase - CHQ.pdf

Statistical analyses

Statistical analysis title	CHQ: Psychosocial subscale (PsS)

Statistical analysis description:

Joint modelling for estimating longitudinal treatment effects adjusted for dropout due to treatment failure.

Comparison groups	Adalimumab (blinded phase) v Placebo (blinded phase)
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.15
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	2.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.44
upper limit	5.4

Statistical analysis title	CHQ: Physical subscale (PhS)

Statistical analysis description:

Joint modelling for estimating longitudinal treatment effects adjusted for dropout due to treatment failure.

Comparison groups	Adalimumab (blinded phase) v Placebo (blinded phase)
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.55
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.16

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.41
upper limit	5.05

Secondary: Blinded phase: Quality of life assessments: Childhood Health Assessment Questionnaire (CHAQ)

End point title	Blinded phase: Quality of life assessments: Childhood Health Assessment Questionnaire (CHAQ)

End point description:

The overall index is calculated by summing the overall scores for each of the categories in the CHAQ and dividing by the number of categories answered. This will give a score between 0 and 3.

Summary tables showing the number of assessments at each time point have been uploaded as a supplementary file.

End point type	Secondary

End point timeframe:

Participants were assessed from randomisation up until:
-time of treatment failure
-completion of 18 months of treatment
-unblinding following TSC decision,
whichever occurred first.

End point values	Adalimumab (blinded phase)	Placebo (blinded phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59[15]	28[16]		
Units: CHAQ				
arithmetic mean (standard deviation)				
Baseline	0.52 (± 0.64)	0.48 (± 0.49)		
1 month	0.41 (± 0.56)	0.60 (± 0.55)		
2 months	0.38 (± 0.53)	0.54 (± 0.59)		
3 months	0.36 (± 0.58)	0.37 (± 0.47)		
6 months	0.36 (± 0.61)	0.46 (± 0.63)		
9 months	0.35 (± 0.63)	0.36 (± 0.57)		
12 months	0.33 (± 0.60)	0.09 (± 0.15)		
15 months	0.43 (± 0.58)	0.03 (± 0.04)		
18 months	0.30 (± 0.48)	0.03 (± 0.05)		

Notes:

[15] - 59 had a baseline assessment.

[16] - 28 had a baseline assessment.

Attachments (see zip file)	Blinded Phase - CHAQ.pdf

Statistical analyses

Statistical analysis title	CHAQ

Statistical analysis description:

Joint modelling for estimating longitudinal treatment effects adjusted for dropout due to treatment failure.

Comparison groups	Adalimumab (blinded phase) v Placebo (blinded phase)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.09
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	0.02

Secondary: Blinded phase: American College of Rheaumatology (ACR) score

End point title	Blinded phase: American College of Rheaumatology (ACR) score

End point description:

The 6 paediatric core set criteria assessed at each study visit are:
Physician global assessment of disease activity (10 cm visual analogue scale).
Parent/patient assessment of overall well-being (10 cm visual analogue scale).
Functional ability (Childhood Health Assessment Questionnaire, CHAQ).
Number of joints with active arthritis.
Number of joints with limited range of movement.
Erythrocyte sedimentation rate.

Summary tables showing the number of assessments at each time point have been uploaded as a supplementary file.
The ACR Paediatric 30, 50, 70, 90 and 100 levels are defined as 30%, 50%, 70%, 90% and 100% improvement, respectively, in a minimum of three variables in the core set with worsening of one variable by no more than 30% as defined in the ACR criteria.

The frequencies below show the number of participants who achieved each ACR level.

End point type	Secondary

End point timeframe:

Participants were assessed from randomisation up until:
-time of treatment failure
-completion of 18 months of treatment
-unblinding following TSC decision,
whichever occurred first.

End point values	Adalimumab (blinded phase)	Placebo (blinded phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46[17]	25[18]		
Units: ACR frequency				
number (not applicable)				
ACR30: 1 month	12	7		
ACR30: 2 months	16	8		

ACR30: 3 months	16	6		
ACR30: 6 months	13	3		
ACR30: 9 months	10	1		
ACR30: 12 months	12	2		
ACR30: 15 months	8	1		
ACR30: 18 months	9	1		
ACR50: 1 month	7	7		
ACR50: 2 months	10	7		
ACR50: 3 months	13	5		
ACR50: 6 months	11	3		
ACR50: 9 months	9	1		
ACR50: 12 months	10	2		
ACR50: 15 months	6	1		
ACR50: 18 months	8	1		
ACR70: 1 month	2	5		
ACR70: 2 months	5	3		
ACR70: 3 months	9	3		
ACR70: 6 months	9	3		
ACR70: 9 months	7	1		
ACR70: 12 months	5	1		
ACR70: 15 months	5	1		
ACR70: 18 months	5	1		
ACR90: 1 month	2	1		
ACR90: 2 months	3	1		
ACR90: 3 months	7	2		
ACR90: 6 months	6	2		
ACR90: 9 months	7	1		
ACR90: 12 months	5	1		
ACR90: 15 months	4	1		
ACR90: 18 months	3	1		
ACR100: 1 month	1	0		
ACR100: 2 months	1	1		
ACR100: 3 months	2	1		
ACR100: 6 months	2	1		
ACR100: 9 months	5	0		
ACR100: 12 months	3	0		
ACR100: 15 months	1	0		
ACR100: 18 months	1	0		

Notes:

[17] - There were 46 participants with a result at 1 month; see supp. tables for totals at later timepoints

[18] - There were 25 participants with a result at 1 month; see supp. tables for totals at later timepoints

Attachments (see zip file)	Blinded Phase - ACR.pdf

Statistical analyses

Statistical analysis title	ACR30

Statistical analysis description:

Joint modelling for estimating longitudinal treatment effects adjusted for dropout.

Comparison groups	Adalimumab (blinded phase) v Placebo (blinded phase)

Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.98
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.37
upper limit	1.59

Statistical analysis title	ACR50
Statistical analysis description:	
Joint modelling for estimating longitudinal treatment effects adjusted for dropout.	
Comparison groups	Adalimumab (blinded phase) v Placebo (blinded phase)
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.37
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.15
upper limit	0.77

Statistical analysis title	ACR70
Statistical analysis description:	
Joint modelling for estimating longitudinal treatment effects adjusted for dropout.	
Comparison groups	Adalimumab (blinded phase) v Placebo (blinded phase)
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.16
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.7
upper limit	0.46

Statistical analysis title	ACR90
Comparison groups	Adalimumab (blinded phase) v Placebo (blinded phase)
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.72
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.22
upper limit	1.39

Statistical analysis title	ACR100
Comparison groups	Adalimumab (blinded phase) v Placebo (blinded phase)
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.65
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.85
upper limit	1.17

Secondary: Blinded phase: Number of participants undergoing disease flares

End point title	Blinded phase: Number of participants undergoing disease flares

End point description:

For this secondary outcome, ‘disease flare’ refers to a flare of arthritis rather than the eye. The definition of ‘disease flare’ is a worsening of 30% or more in 3 or more of the 6 variables of the JIA core set , with no more than one variable improving by 30% or more.

End point type	Secondary

End point timeframe:

Participants were assessed from randomisation up until:
-time of treatment failure
-completion of 18 months of treatment
-unblinding following TSC decision,
whichever occurred first.

End point values	Adalimumab (blinded phase)	Placebo (blinded phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	30		
Units: Events				
Disease flare	0	3		
No disease flare	60	27		

Statistical analyses

Statistical analysis title	Disease flare
Comparison groups	Adalimumab (blinded phase) v Placebo (blinded phase)
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.004
upper limit	1.36

Secondary: Blinded phase: Number of participants with minimum disease activity

End point title	Blinded phase: Number of participants with minimum disease activity

End point description:

Minimum disease activity is defined for those with Oligoarthritis and Polyarthritis.

End point type	Secondary

End point timeframe:

Participants were assessed from randomisation up until:
-time of treatment failure
-completion of 18 months of treatment
-unblinding following TSC decision,
whichever occurred first.

End point values	Adalimumab (blinded phase)	Placebo (blinded phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59[19]	29[20]		
Units: Events				
Minimum disease activity	19	4		
No minimum disease activity	40	25		

Notes:

[19] - There were 59 participants with Oligoarticular JIA or Polyarticular JIA.

[20] - There were 29 participants with Oligoarticular JIA or Polyarticular JIA.

Statistical analyses

Statistical analysis title	Minimum disease activity
Comparison groups	Adalimumab (blinded phase) v Placebo (blinded phase)
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.08
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	2.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	6.24

Secondary: Blinded phase: Number of participants requiring change in biologic and/or DMARD therapy for arthritis due to failure to respond

End point title	Blinded phase: Number of participants requiring change in biologic and/or DMARD therapy for arthritis due to failure to respond

End point description:

DMARDs are disease-modifying anti-rheumatic drugs.

End point type	Secondary

End point timeframe:

Participants were assessed for treatment failure from randomisation up until:
-time of treatment failure
-completion of 18 months of treatment
-unblinding following TSC decision,
whichever occurred first.

End point values	Adalimumab (blinded phase)	Placebo (blinded phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	30		
Units: Events				
Change in therapy	2	1		
No change in therapy	58	29		

Statistical analyses

Statistical analysis title	Number of participants requiring change in DMARDs
Comparison groups	Adalimumab (blinded phase) v Placebo (blinded phase)
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.99
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	5.09

Secondary: Blinded phase: Participants score of the Juvenile Arthritis Disease Activity Score (JADAS)

End point title	Blinded phase: Participants score of the Juvenile Arthritis Disease Activity Score (JADAS)

End point description:

The JADAS is comprised of four components:
-physician global assessment of disease activity,
-parent/patient global assessment of well-being,
-active joint count, in 27, 71 or 10 joints,
-erythrocyte sedimentation rate (ESR).

The JADAS is calculated as a sum of scores giving global scores of 0-57, 0-101 and 0-40 for the JADAS-27, JADAS-71 and JADAS-10 respectively.

Summary tables showing the number of assessments at each time point have been uploaded as a supplementary file.

End point type	Secondary

End point timeframe:

Participants were assessed from randomisation up until:
-time of treatment failure
-completion of 18 months of treatment
-unblinding following TSC decision,
whichever occurred first.

End point values	Adalimumab (blinded phase)	Placebo (blinded phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	30		
Units: JADAS				
arithmetic mean (standard deviation)				
JADAS10: Baseline	3.48 (± 4.20)	4.51 (± 5.61)		
JADAS10: 1 month	2.03 (± 2.31)	3.12 (± 3.84)		
JADAS10: 2 months	1.62 (± 2.29)	3.72 (± 5.76)		
JADAS10: 3 months	1.54 (± 2.13)	3.56 (± 4.64)		
JADAS10: 6 months	1.78 (± 2.44)	3.02 (± 3.80)		
JADAS10: 9 months	1.12 (± 1.51)	1.42 (± 1.24)		
JADAS10: 12 months	1.46 (± 2.35)	0.20 (± 0.26)		
JADAS10: 15 months	1.07 (± 1.28)	1.33 (± 0.97)		
JADAS10: 18 months	1.62 (± 1.94)	1.50 (± 1.31)		
JADAS27: Baseline	3.29 (± 3.89)	3.65 (± 4.41)		
JADAS27: 1 month	1.92 (± 1.94)	2.59 (± 2.71)		
JADAS27: 2 months	1.62 (± 2.29)	3.43 (± 5.40)		
JADAS27: 3 months	1.49 (± 1.97)	3.25 (± 4.04)		
JADAS27: 6 months	1.73 (± 2.34)	3.02 (± 3.80)		
JADAS27: 9 months	1.12 (± 1.51)	1.42 (± 1.24)		
JADAS27: 12 months	1.46 (± 2.35)	0.20 (± 0.26)		
JADAS27: 15 months	1.02 (± 1.24)	1.33 (± 0.97)		
JADAS27: 18 months	1.62 (± 1.94)	1.50 (± 1.31)		
JADAS71: Baseline	3.54 (± 4.43)	4.24 (± 5.95)		
JADAS71: 1 month	2.03 (± 2.31)	3.29 (± 4.38)		
JADAS71: 2 months	1.62 (± 2.29)	3.72 (± 5.76)		
JADAS71: 3 months	1.54 (± 2.13)	3.79 (± 5.23)		
JADAS71: 6 months	1.78 (± 2.44)	3.02 (± 3.80)		
JADAS71: 9 months	1.12 (± 1.51)	1.42 (± 1.24)		
JADAS71: 12 months	1.46 (± 2.35)	0.20 (± 0.26)		
JADAS71: 15 months	1.07 (± 1.28)	1.33 (± 0.97)		
JADAS71: 18 months	1.62 (± 1.94)	1.50 (± 1.31)		

Attachments (see zip file)	Blinded Phase - JADAS.pdf

Statistical analyses

Statistical analysis title	JADAS10
Statistical analysis description: Joint modelling for estimating longitudinal treatment effects adjusted for dropout.	
Comparison groups	Adalimumab (blinded phase) v Placebo (blinded phase)
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.07
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.35

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.78
upper limit	0.01

Statistical analysis title	JADAS27
Statistical analysis description:	
Joint modelling for estimating longitudinal treatment effects adjusted for dropout.	
Comparison groups	Adalimumab (blinded phase) v Placebo (blinded phase)
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.08
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.76
upper limit	0.03

Statistical analysis title	JADAS71
Comparison groups	Adalimumab (blinded phase) v Placebo (blinded phase)
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.07
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.78
upper limit	0.004

Secondary: Blinded phase: Compliance according to participant diaries

End point title	Blinded phase: Compliance according to participant diaries

End point description:

Treatment diaries were used to estimate participant compliance by dividing the number of doses recorded as taken in the treatment diary by the expected number of doses the participant should have taken (according to the time the participant was on treatment). No formal statistical analysis was

undertaken.

End point type	Secondary

End point timeframe:

Participants were assessed from randomisation up until:
-withdrawal
-time of treatment failure
-completion of 18 months of treatment
-unblinding following TSC decision,
whichever occurred first.

End point values	Adalimumab (blinded phase)	Placebo (blinded phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	30		
Units: percent				
number (not applicable)				
Compliance	84	74		

Statistical analyses

No statistical analyses for this end point

Secondary: Blinded phase: Compliance according to accountability logs

End point title	Blinded phase: Compliance according to accountability logs

End point description:

Accountability logs were used to provide another estimate of adalimumab and placebo compliance by dividing the sum of the number of vials returned used and the number of missing vials, by the number of vials issued.

End point type	Secondary

End point timeframe:

Participants were assessed from randomisation up until:
-withdrawal
-time of treatment failure
-completion of 18 months of treatment
-unblinding following TSC decision,
whichever occurred first.

End point values	Adalimumab (blinded phase)	Placebo (blinded phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	30		
Units: percent				
number (not applicable)				
Compliance	94	90		

Statistical analyses

No statistical analyses for this end point

Secondary: Blinded phase: Laboratory parameters

End point title	Blinded phase: Laboratory parameters

End point description:

The parameters reported on for haematological assessments are:
-Heamatocrit
-Haemoglobin
-Red blood cell count
-White blood cell count
-Neutrophils
-Lymphocytes
-Monocytes
-Basophils
-Eosinophils
-Platelet count
-Erythrocyte sedimentation rate
-Plasma viscosity (only done if ESR not available

The parameters reported on for biochemical assessments are:
-C- Reactive protein (CRP)
-Urea
-Creatinine
-Sodium
-Potassium
-Calcium
-Inorganic phosphate
-Glucose
-Chloride
-Bicarbonate
-Total bilirubin
-Alanine aminotransferase (ALT)
-Aspartate aminotransferase (AST)

The parameters reported on for urinalysis are:
-Protein
-Glucose
-Blood
-Leukocyte esterase
-Specific gravity
-pH

Supplementary tables summarising the data have been uploaded.

End point type	Secondary

End point timeframe:

Participants were assessed from randomisation up until:
-time of treatment failure
-completion of 18 months of treatment
-unblinding following TSC decision,
whichever occurred first.

End point values	Adalimumab (blinded phase)	Placebo (blinded phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	30		
Units: See supplementary tables.	60	30		

Attachments (see zip file)	Blinded Phase - Laboratory Parameters.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Blinded phase: Incremental cost-effectiveness and cost utility

End point title	Blinded phase: Incremental cost-effectiveness and cost utility

End point description:

End point type	Secondary

End point timeframe:

This analysis is reported separately by Health Economists at the Universtiy of Bangor. See HTA report for full details upon publication.

End point values	Adalimumab (blinded phase)	Placebo (blinded phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	30		
Units: Unit costs	60	30		

Statistical analyses

No statistical analyses for this end point

Secondary: Follow-up phase: Use of corticosteroids over duration of study period (blinded, open label and follow up phase)

End point title	Follow-up phase: Use of corticosteroids over duration of study period (blinded, open label and follow up phase)

End point description:

The total dose is calculated separately for the treatment phase and follow -up period, by summing the daily doses of each oral treatment on the Concomitant Medication Form taken during each period.

The total dose for each time- period of interest (treatment, follow -up and whole trial) should be summed across each treatment arm and standardised to per patient years for that treatment. This is calculated by dividing the total oral dose in each arm by the cumulative years all patients in the corresponding arm are on treatment for.

End point type	Secondary

End point timeframe:

Duration of study period (blinded, open-label and follow-up phase).

End point values	Adalimumab (follow-up)	Placebo (follow-up)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[21]	1[22]		
Units: miligrams per patient year				
number (not applicable)				
Total dose per patient years	790.27	3767.74		

Notes:

[21] - 5 participants were taking oral corticosteroids at randomisation.

[22] - 1 participant was taking oral corticosteroids at randomisation.

Statistical analyses

Statistical analysis title	Total oral corticosteroid dose
Comparison groups	Adalimumab (follow-up) v Placebo (follow-up)
Number of subjects included in analysis	6
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Poisson regression
Parameter estimate	Rate ratio
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	0.23

Secondary: Follow-up phase: Reduction in systemic corticosteroid dose from entry dose to 0mg

End point title	Follow-up phase: Reduction in systemic corticosteroid dose from entry dose to 0mg

End point description:

Reduction in systemic corticosteroid dose from entry dose to 0mg from randomisation to end of trial.

It was not possible to undertake this analysis due to the fact that the statistical algorithm did not converge.

End point type	Secondary

End point timeframe:

Participants were assessed from randomisation to the end of the trial.

End point values	Adalimumab (follow-up)	Placebo (follow-up)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[23]	1[24]		
Units: Events				
Reduced dose	5	1		
Censored	0	0		

Notes:

[23] - At baseline 5 participants were prescribed systemic corticosteroids >0mg.

[24] - At baseline 1 participant was prescribed systemic corticosteroids >0mg.

Statistical analyses

No statistical analyses for this end point

Secondary: Follow-up phase: Reduction in systemic corticosteroid dose from entry dose to <5mg

End point title	Follow-up phase: Reduction in systemic corticosteroid dose from entry dose to <5mg

End point description:

Reduction in systemic corticosteroid dose from entry dose to less than 5mg from randomisation to end of trial.

It was not possible to undertake the analysis as the statistical algorithm did not converge.

End point type	Secondary

End point timeframe:

Participants were assessed from randomisation to the end of the trial.

End point values	Adalimumab (follow-up)	Placebo (follow-up)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2[25]	1[26]		
Units: Events				
Reduced dose	2	1		
Censored	0	0		

Notes:

[25] - At baseline 2 participants were prescribed systemic corticosteroids >=5mg.

[26] - At baseline 1 participant was prescribed systemic corticosteroids >=5mg.

Statistical analyses

No statistical analyses for this end point

Secondary: Follow-up phase: Time to reduction to <2 drops in topical corticosteroids

End point title	Follow-up phase: Time to reduction to <2 drops in topical corticosteroids

End point description:

See blinded phase for full description of end-point.

End point type	Secondary

End point timeframe:

Participants were assessed from randomisation to the end of the trial.

End point values	Adalimumab (follow-up)	Placebo (follow-up)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45[27]	18[28]		
Units: Events				
Reduced drops	27	3		
Censored	18	15		

Notes:

[27] - There were 45 participants who were on >=2 drops at baseline.

[28] - There were 18 participants who were on >=2 drops at baseline.

Statistical analyses

Statistical analysis title	Time to reduction to <2 drops

Statistical analysis description:

This was a competing risks analysis, accounting for the time to treatment failure.

Comparison groups	Adalimumab (follow-up) v Placebo (follow-up)
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012
Method	Fine and Gray
Parameter estimate	Hazard ratio (HR)
Point estimate	4.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.41
upper limit	16

Secondary: Follow-up phase: Need for pulsed corticosteroid

End point title	Follow-up phase: Need for pulsed corticosteroid

End point description:

See blinded phase for full description of end-point.

End point type	Secondary

End point timeframe:

Participants were assessed from randomisation to the end of trial.

End point values	Adalimumab (follow-up)	Placebo (follow-up)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	29		
Units: Events				
Needed pulsed corticosteroids	4	1		
Did not need pulsed corticosteroids	54	28		

Statistical analyses

Statistical analysis title	Need for pulsed corticosteroids
Comparison groups	Placebo (follow-up) v Adalimumab (follow-up)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.66
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	17.12

Secondary: Follow-up phase: Laboratory parameters

End point title	Follow-up phase: Laboratory parameters
End point description:	
Supplementary tables summarising the data have been uploaded.	
End point type	Secondary
End point timeframe:	
Participants were followed up for a maximum of 18 months post treatment.	

End point values	Adalimumab (follow-up)	Placebo (follow-up)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	29		
Units: See supplementary tables.	58	29		

Attachments (see zip file)	Follow-up Phase - Laboratory Parameters.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Blinded phase: Reduction in systemic corticosteroid dose from entry dose to <5mg

End point title	Blinded phase: Reduction in systemic corticosteroid dose from entry dose to <5mg

End point description:

Reduction in systemic corticosteroid dose from entry dose to <5mg will be analysed for a subset of patients, as not everyone will be taking systemic corticosteroids at randomisation.

End point type	Secondary

End point timeframe:

Participants were assessed from randomisation up until:
-time of treatment failure
-completion of 18 months of treatment
-unblinding,
whichever occurred first.

End point values	Adalimumab (blinded phase)	Placebo (blinded phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2[29]	1[30]		
Units: Events				
Reduced dose	1	1		
Censored	1	0		

Notes:

[29] - 2 participants were prescribed systemic corticosteroids >=5mg at baseline.

[30] - 1 participant was prescribed systemic corticosteroids >=5mg at baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Follow-up phase: Rate of systemic corticosteroid dose from entry dose

End point title	Follow-up phase: Rate of systemic corticosteroid dose from entry dose

End point description:

The total dose is calculated by summing the daily doses and standardised to per patient years.

End point type	Secondary

End point timeframe:

Participants were assessed from randomisation to end of trial.

End point values	Adalimumab (follow-up)	Placebo (follow-up)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[31]	1[32]		
Units: miligrams per patient year				
number (not applicable)				
Total dose per patient years	790.27	3767.74		

Notes:

[31] - 5 participants were taking oral corticosteroids at randomisation.

[32] - 1 participant was taking oral corticosteroids at randomisation.

Statistical analyses

Statistical analysis title	Rate of systemic corticosteroid dose
Comparison groups	Placebo (follow-up) v Adalimumab (follow-up)
Number of subjects included in analysis	6
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Poisson regression
Parameter estimate	Rate ratio
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	0.23

Post-hoc: Blinded phase: Time to reduction to 0 drops in topical corticosteroids

End point title	Blinded phase: Time to reduction to 0 drops in topical corticosteroids

End point description:

This outcome is the time to reduction to 0 drops for those patients already on >0 drop at randomisation.

End point type	Post-hoc

End point timeframe:

Participants were assessed for treatment failure from randomisation up until:
-time of treatment failure
-completion of 18 months of treatment
-unblinding following TSC decision,
whichever occurred first.

End point values	Adalimumab (blinded phase)	Placebo (blinded phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49[33]	25[34]		
Units: Events				
number (not applicable)				
Events	25	4		
Censored	24	21		

Notes:

[33] - 49 participants were on >0 drops at randomisation.

[34] - 25 participants were on >0 drops at randomisation.

Statistical analyses

Statistical analysis title	Time to reduction to 0 drops

Statistical analysis description:

This was a competing risks analysis, accounting for the time to treatment failure.

Comparison groups	Adalimumab (blinded phase) v Placebo (blinded phase)
Number of subjects included in analysis	74
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.01
Method	Fine and Gray
Parameter estimate	Hazard ratio (HR)
Point estimate	4.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.4
upper limit	11.5

Post-hoc: Follow-up phase: Time to reduction to 0 drops in topical corticosteroid

End point title	Follow-up phase: Time to reduction to 0 drops in topical corticosteroid

End point description:

This outcome is the time to reduction to 0 drops for those patients already on >0 drops at randomisation.

End point type	Post-hoc

End point timeframe:

Participants were assessed from randomisation to the end of the trial.

End point values	Adalimumab (follow-up)	Placebo (follow-up)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49[35]	25[36]		
Units: Events				
Reduced drops	30	4		
Censored	19	21		

Notes:

[35] - 49 participants were on >= 0 drops per day at baseline.

[36] - 25 participants were on >= 0 drops per day at baseline.

Statistical analyses

Statistical analysis title	Time to reduction to 0 drops
Comparison groups	Adalimumab (follow-up) v Placebo (follow-up)
Number of subjects included in analysis	74
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0022
Method	Fine and Gray
Parameter estimate	Hazard ratio (HR)
Point estimate	5.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.82
upper limit	15.1

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were collected up to 30 days following treatment cessation.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18

Reporting groups	
Reporting group title	Adalimumab
Reporting group description:	
Adalimumab subcutaneous injection every 2 weeks for 18 months.	
Reporting group title	Placebo
Reporting group description:	
Placebo subcutaneous injection every 2 weeks for 18 months	

Serious adverse events	Adalimumab	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 60 (23.33%)	2 / 30 (6.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Surgical and medical procedures			
Antiviral prophylaxis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Testes exploration			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Anterior chamber flare			

subjects affected / exposed	0 / 60 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uveitis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food poisoning			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (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			
Tonsillar hypertrophy			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Joint swelling	Additional description: This SAE occurred during follow-up and outside the reporting timelines as stated in the SYCAMORE protocol.		
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			

subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected bite			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scarlet fever			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal infection			
subjects affected / exposed	2 / 60 (3.33%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella			
subjects affected / exposed	2 / 60 (3.33%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	2 / 60 (3.33%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Adalimumab	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 60 (100.00%)	26 / 30 (86.67%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	5 / 60 (8.33%)	0 / 30 (0.00%)	
occurrences (all)	5	0	
Surgical and medical procedures			
Tonsillectomy			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Crying			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Drug intolerance			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	1 / 60 (1.67%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Feeling hot			
subjects affected / exposed	0 / 60 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Hangover			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Influenza like illness			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Injection site bruising			

subjects affected / exposed	2 / 60 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	3	0	
Injection site erythema			
subjects affected / exposed	3 / 60 (5.00%)	1 / 30 (3.33%)	
occurrences (all)	4	1	
Injection site mass			
subjects affected / exposed	2 / 60 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	8	0	
Injection site pain			
subjects affected / exposed	5 / 60 (8.33%)	2 / 30 (6.67%)	
occurrences (all)	15	5	
Injection site pruritus			
subjects affected / exposed	3 / 60 (5.00%)	0 / 30 (0.00%)	
occurrences (all)	3	0	
Injection site reaction			
subjects affected / exposed	8 / 60 (13.33%)	0 / 30 (0.00%)	
occurrences (all)	40	0	
Injection site swelling			
subjects affected / exposed	4 / 60 (6.67%)	1 / 30 (3.33%)	
occurrences (all)	9	1	
Injection site vesicles			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Malaise			
subjects affected / exposed	2 / 60 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	3	0	
Pain			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Pyrexia			
subjects affected / exposed	15 / 60 (25.00%)	3 / 30 (10.00%)	
occurrences (all)	39	6	
Swelling			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			

Immunisation reaction			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Seasonal allergy			
subjects affected / exposed	3 / 60 (5.00%)	1 / 30 (3.33%)	
occurrences (all)	3	1	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	7	0	
Pruritus genital			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Vaginal lesion			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal pruritus			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Adenoidal disorder			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Asthma			
subjects affected / exposed	1 / 60 (1.67%)	1 / 30 (3.33%)	
occurrences (all)	1	2	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	22 / 60 (36.67%)	3 / 30 (10.00%)	
occurrences (all)	32	3	
Dyspnoea			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	

Epistaxis			
subjects affected / exposed	3 / 60 (5.00%)	0 / 30 (0.00%)	
occurrences (all)	5	0	
Nasal congestion			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Nasal discomfort			
subjects affected / exposed	2 / 60 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	4	0	
Oropharyngeal pain			
subjects affected / exposed	19 / 60 (31.67%)	2 / 30 (6.67%)	
occurrences (all)	43	3	
Productive cough			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Sinus congestion			
subjects affected / exposed	2 / 60 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Snoring			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Wheezing			
subjects affected / exposed	0 / 60 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 60 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Agitation			
subjects affected / exposed	0 / 60 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Anxiety			

subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Emotional distress			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Irritability			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 60 (10.00%)	1 / 30 (3.33%)	
occurrences (all)	11	1	
Aspartate aminotransferase abnormal			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 60 (8.33%)	1 / 30 (3.33%)	
occurrences (all)	6	1	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Blood glucose abnormal			
subjects affected / exposed	0 / 60 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Blood potassium increased			
subjects affected / exposed	2 / 60 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
C-reactive protein abnormal			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
C-reactive protein increased			
subjects affected / exposed	2 / 60 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Haematocrit abnormal			

subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Haemoglobin decreased			
subjects affected / exposed	0 / 60 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Intraocular pressure increased			
subjects affected / exposed	4 / 60 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	7	0	
Liver function test abnormal			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Neutrophil count decreased			
subjects affected / exposed	0 / 60 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Red blood cell count abnormal			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Red blood cell sedimentation rate abnormal			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Red blood cell sedimentation rate increased			
subjects affected / exposed	4 / 60 (6.67%)	1 / 30 (3.33%)	
occurrences (all)	5	1	
Rubulavirus test positive			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Urine protein/creatinine ratio abnormal			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Vitamin D decreased			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			

Animal bite			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Arthropod bite			
subjects affected / exposed	2 / 60 (3.33%)	1 / 30 (3.33%)	
occurrences (all)	2	2	
Arthropod sting			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Bite			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Contusion			
subjects affected / exposed	2 / 60 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Fall			
subjects affected / exposed	4 / 60 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	4	0	
Injury			
subjects affected / exposed	0 / 60 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Joint dislocation			
subjects affected / exposed	0 / 60 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	2	
Joint injury			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Laceration			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Ligament sprain			
subjects affected / exposed	2 / 60 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Upper limb fracture			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	

Foreign body			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	15 / 60 (25.00%)	4 / 30 (13.33%)	
occurrences (all)	26	10	
Hypoaesthesia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Hyposmia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Migraine			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	3	0	
Paraesthesia			
subjects affected / exposed	2 / 60 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	3	0	
Psychomotor hyperactivity			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Increased tendency to bruise			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Lymphadenopathy			
subjects affected / exposed	3 / 60 (5.00%)	0 / 30 (0.00%)	
occurrences (all)	3	0	
Neutropenia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Eye disorders			

Dry eye			
subjects affected / exposed	2 / 60 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Eye discharge			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Eye inflammation			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Eye swelling			
subjects affected / exposed	2 / 60 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Eyelid oedema			
subjects affected / exposed	0 / 60 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Glaucoma			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Iridocyclitis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Iris disorder			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Photopsia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Uveitis			
subjects affected / exposed	4 / 60 (6.67%)	4 / 30 (13.33%)	
occurrences (all)	4	4	
Vision blurred			
subjects affected / exposed	1 / 60 (1.67%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Visual impairment			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	

Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			
subjects affected / exposed	3 / 60 (5.00%)	0 / 30 (0.00%)	
occurrences (all)	4	0	
Abdominal pain upper			
subjects affected / exposed	2 / 60 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	4	0	
Constipation			
subjects affected / exposed	2 / 60 (3.33%)	2 / 30 (6.67%)	
occurrences (all)	2	3	
Dental caries			
subjects affected / exposed	2 / 60 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Diarrhoea			
subjects affected / exposed	7 / 60 (11.67%)	1 / 30 (3.33%)	
occurrences (all)	11	1	
Dyspepsia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Haematochezia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Haemorrhoids			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	6 / 60 (10.00%)	2 / 30 (6.67%)	
occurrences (all)	10	2	
Stomatitis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Toothache			

subjects affected / exposed	3 / 60 (5.00%)	0 / 30 (0.00%)	
occurrences (all)	4	0	
Vomiting			
subjects affected / exposed	19 / 60 (31.67%)	6 / 30 (20.00%)	
occurrences (all)	43	8	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 60 (1.67%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Dermatitis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Ingrowing nail			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Night sweats			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 60 (1.67%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Rash			
subjects affected / exposed	3 / 60 (5.00%)	2 / 30 (6.67%)	
occurrences (all)	6	2	
Rash papular			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Swelling face			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	13 / 60 (21.67%)	2 / 30 (6.67%)	
occurrences (all)	25	3	
Arthritis			
subjects affected / exposed	1 / 60 (1.67%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Back pain			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Joint stiffness			
subjects affected / exposed	1 / 60 (1.67%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Joint swelling			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Juvenile idiopathic arthritis			
subjects affected / exposed	0 / 60 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Pain in extremity			
subjects affected / exposed	2 / 60 (3.33%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
Pain in jaw			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Candida infection			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Cestode infection			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis			
subjects affected / exposed	3 / 60 (5.00%)	0 / 30 (0.00%)	
occurrences (all)	3	0	
Conjunctivitis viral			

subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Ear infection			
subjects affected / exposed	7 / 60 (11.67%)	2 / 30 (6.67%)	
occurrences (all)	8	2	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Eye infection			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Herpes simplex			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	6	0	
Herpes zoster			
subjects affected / exposed	0 / 60 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Impetigo			
subjects affected / exposed	4 / 60 (6.67%)	1 / 30 (3.33%)	
occurrences (all)	5	1	
Infected bite			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Infection			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Localised infection			
subjects affected / exposed	0 / 60 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Lower respiratory tract infection			
subjects affected / exposed	8 / 60 (13.33%)	2 / 30 (6.67%)	
occurrences (all)	9	4	
Molluscum contagiosum			

subjects affected / exposed	2 / 60 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Nasopharyngitis			
subjects affected / exposed	17 / 60 (28.33%)	8 / 30 (26.67%)	
occurrences (all)	29	10	
Oral herpes			
subjects affected / exposed	3 / 60 (5.00%)	1 / 30 (3.33%)	
occurrences (all)	3	1	
Otitis media			
subjects affected / exposed	1 / 60 (1.67%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Paronychia			
subjects affected / exposed	3 / 60 (5.00%)	1 / 30 (3.33%)	
occurrences (all)	3	1	
Pharyngitis			
subjects affected / exposed	4 / 60 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	4	0	
Pneumonia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Rhinitis			
subjects affected / exposed	2 / 60 (3.33%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
Rubella			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Skin infection			
subjects affected / exposed	2 / 60 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Staphylococcal infection			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Streptococcal infection			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Tonsillitis			

subjects affected / exposed	13 / 60 (21.67%)	0 / 30 (0.00%)	
occurrences (all)	24	0	
Tonsillitis streptococcal			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	5 / 60 (8.33%)	1 / 30 (3.33%)	
occurrences (all)	8	1	
Urethritis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	10 / 60 (16.67%)	3 / 30 (10.00%)	
occurrences (all)	13	4	
Varicella			
subjects affected / exposed	2 / 60 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Viral infection			
subjects affected / exposed	11 / 60 (18.33%)	1 / 30 (3.33%)	
occurrences (all)	15	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 60 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Dehydration			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 September 2011	The first amendment to the protocol made corrections to typographical errors in the original protocol.
30 September 2011	The second amendment added clarification to the Tissue Bank section, clarification to the primary endpoint section and introduction of endpoint for intermittent or continuous suspension of adalimumab/placebo, clarification that patients cannot have previously received adalimumab, addition of two further exclusion criteria points relating to intra-ocular pressure, removal of limit on how many times patients can be screened, addition of window for adalimumab/placebo injections, clarification of topical treatment after 3 months trial treatment, change to dose range of allowed methotrexate to 10-20mg/m2 and clarification of treatment timelines and visit windows.
25 April 2013	The third amendment to the protocol made changes to the monthly visit windows to allow a window of 7 days, clarified in the table of assessments that CSRI questionnaire is completed at baseline only, changed the timeline for tuberculosis assessment from 4 weeks to 12 weeks prior to baseline and clarified that haematological and biochemical samples taken at screening can be used for the baseline visit.
25 September 2013	The fourth amendment to the protocol reduced the sample size from 154 to 114 and the duration of follow up post treatment from 18 months to 6 months, changed the assessment of reduction of vision from number of letters to LogMAR units, clarification to inclusion and exclusion criteria, addition of systemic acetazolamide as medication not permitted, removal of the collection of human anti-human antibody samples, window for methotrexate administration added, change to the collection of routine patient-level information and costing systems (PLICS) data and clarification on definition of end of trial added.
11 August 2014	The fifth amendment to the protocol added text to say that the IDSMC may request an interim analysis of the primary outcome.
11 August 2014	The sixth change to the protocol clarified that patients are classed as withdrawals and not treatment failures if they miss more than 4 weeks of methotrexate treatment, added further clarification that haematological and biochemical blood results can be used for baseline if taken at screening only if assessment was completed within the previous 15 days, clarification added to Tissue Bank samples to state that 3 months sample should be taken at the very next opportunity if not taken at 3 months and that the 18 months samples should be taken if patient ends treatment early.
17 April 2015	The seventh change to the protocol stated that the blinded phase of the trial has been stopped, all patients on adalimumab will continue to be treated but patients on placebo will stop treatment and proceed to follow up.
14 July 2016	The eighth change to the protocol clarified that JADAS was a secondary outcome and SAE reporting procedures.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
17 April 2015	Following the results of an interim analysis, the IDSMC recommended that recruitment to SYCAMORE stop and the allocations of patients who were currently in the trial be unblinded. They recommended that patients who were on placebo stop taking the allocated treatment and enter the 6 month follow-up period of the trial (treatment of these patients was then at the discretion of the treating clinician). Patients who were on adalimumab were to continue on their allocated treatment as per protocol in an 'open label' fashion. Following completion of this 'open label' period, adalimumab patients entered the 6 month follow-up period. The IDSMC recommended that the results of the double blind period be made publically available. On the 17th April 2015, following the IDSMC recommendation, the TSC made the decision to unblind the trial.	-

Notes:

Limitations and caveats

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

N/A

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28445659