Clinical trial results:
A phase II trial of Tocilizumab in anti-TNF refractory patients with JIA associated uveitis.

Summary

EudraCT number	2015-001323-23
Trial protocol	GB
Global end of trial date	28 September 2018

Results information

Result version number	v1 (current)
This version publication date	05 October 2019
First version publication date	05 October 2019
Summary attachment (see zip file)	Baseline characteristics (Baseline disease characteristics.pdf)

Trial information

Trial identification

Sponsor protocol code	CH/2013/4247

Additional study identifiers

ISRCTN number	ISRCTN95363507
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	AR UK ref: 20659

Notes:

Sponsors

Sponsor organisation name	University Hospitals Bristol NHS Foundation Trust
Sponsor organisation address	Upper Maudlin Street, Bristol, United Kingdom, BS2 8AE
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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	22 March 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 June 2018
Global end of trial reached?	Yes
Global end of trial date	28 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial is to estimate the clinical response rate of uveitis to Tocilizumab in combination with MTX in children with JIA-associated uveitis who have failed anti-TNF therapy, and to determine whether further research into the use of this intervention for the treatment of anti-TNF refractory JIA-associated uveitis should be conducted.

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 APITUDE.

Background therapy:

All subjects to receive a stable dose of methotrexate.

Evidence for comparator:

Tocilizumab (trade name RoActemra) is also a biological therapy blocking the action of interleukin (IL)-6. In arthritis, IL-6 causes tiredness, anaemia, and inflammation and damage to bones, cartilage and tissue. Tocilizumab reduces these effects. Previous studies looking at the effect of Tocilizumab in children have been conducted looking at Rheumatology examinations only. However trial of Tocilizumab in children with the systemic form of JIA have responded dramatically to this treatment in a short time span and became the first drug licenced for use in JIA in fifty years, obtaining NICE approval for this indication. It is also being trialled at present in polyarticular forms of JIA with good effect. However these clinical trials for Tocilizumab state that a diagnosis of Uveitis is part of the exclusion criteria.

Actual start date of recruitment	04 November 2015
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: 21
Worldwide total number of subjects	21
EEA total number of subjects	21

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)	8
Adolescents (12-17 years)	13
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 7 United Kingdom centres.

Pre-assignment

Screening details:

There was a total of 58 screenings assessed for eligibility. 22 were eligible and consented, one patient was immediately found to be ineligible and was therefore withdrawn from the study.

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Tocilizumab

Arm description:

2-3 weekly injections of Tocilizumab with Methotrexate.

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

Dosage and administration details:

Patients received Tocilizumab dosed according to body weight (BW):

Patients weighing ≥ 30 kg dosed with 162 mg of Tocilizumab every two weeks

Patients weighing < 30 kg dosed with 162 mg of Tocilizumab every three weeks

Tocilizumab was supplied in a single use pre-filled syringe fitted into a needle safety device. After removing the pre-filled syringe from the refrigerator the pre-filled syringe was allowed to reach room temperature (18°C to 28C°) by waiting for 25 to 30 minutes, before injecting Tocilizumab. The syringe should not be shaken. After removing the cap the injection must be started within five minutes, to prevent the medicine from drying out and blocking the needle. If the pre-filled syringe was not used within five minutes of removing the cap, it must be disposed of in a puncture resistant container and then a new pre-filled syringe should be used.

Number of subjects in period 1	Tocilizumab
Started	21
Completed	21

Baseline characteristics

Reporting groups	
Reporting group title	Overall

Reporting group description:

2-3 weekly injections of Tocilizumab in combination with Methotrexate. The dosage was calculated based on patient body weight.

Response to treatment was assessed after 12 weeks.

Reporting group values	Overall	Total	
Number of subjects	21	21	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	8	8	
Adolescents (12-17 years)	13	13	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	12.3		
standard deviation	± 3.5	-	
Gender categorical Units: Subjects			
Female	18	18	
Male	3	3	
Weight (kg) Units: Subjects			
<30kg	6	6	
>=30kg	15	15	
Rheumatoid baseline data - Type of JIA (ILAR classification)			
At individual level (all centres)			
Units: Subjects			
Extended oligoarthritis	6	6	
Persistent oligoarthritis	7	7	
Polyarthritis RF negative	7	7	
Psoriatic arthritis	1	1	
Rheumatoid baseline data - Anti-nuclear antibody (ANA)			
At individual level (all centres)			
Units: Subjects			
Negative	5	5	
Positive	15	15	

Not done	1	1	
Rheumatoid baseline data - Double-stranded deoxyribonucleic acid (DsDNA)			
At individual level (all centres)			
Units: Subjects			
Negative	18	18	
Positive	3	3	
Rheumatoid baseline data - Extractable nuclear antigen			
At individual level (all centres)			
Units: Subjects			
Positive	1	1	
Negative	16	16	
Not done	4	4	
Number of study eyes Units: Subjects			
Unilateral	13	13	
Bilateral	8	8	
Rheumatoid baseline data - Disease duration			
At individual level (all centres)			
Units: years			
arithmetic mean	9		
standard deviation	± 4.4	-	
Rheumatoid baseline data - Physician global assessment of disease activity			
At individual level (all centres)			
Units: Assessment score			
arithmetic mean	2		
standard deviation	± 2	-	
Rheumatoid baseline data - Active joint count (all joints)			
At individual level (all centres)			
Units: Joint count			
arithmetic mean	0.9		
standard deviation	± 1.7	-	
Rheumatoid baseline data - Swollen joint count			
At individual level (all centres)			
Units: Joint count			
arithmetic mean	1.1		
standard deviation	± 1.9	-	

End points

End points reporting groups

Reporting group title	Tocilizumab

Reporting group description:

2-3 weekly injections of Tocilizumab with Methotrexate.

Primary: Treatment response

End point title	Treatment response[1]

End point description:

Response to treatment is defined as per SUN criteria as a 2 step decrease in the level of inflammation (anterior chamber cells) or decrease to zero between baseline (prior to trial treatment initiation) and after 12 weeks of treatment.

End point type	Primary

End point timeframe:

Patients were assessed for treatment response after 12 weeks of treatment.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analyses have been added as a supplementary document.

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	21[2]			
Units: Subjects				
Treatment Response	7			
Treatment Failure	14			

Notes:

[2] - One patient was excluded straight after registration

Attachments (see zip file)	Treatment response.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Total oral corticosteorid dose - treatment period

End point title	Total oral corticosteorid dose - treatment period

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 registration up until:
- withdrawal
-time of 'no response'
- completion of treatment,
whichever came first

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	4[3]			
Units: mg standardised to per patient year				
arithmetic mean (confidence interval 95%)	295.29 (263.46 to 330.97)			

Notes:

[3] - There were only 4 patients on oral steroids at the beginning of the study

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction in topical corticosteroids from entry dose: Time to reduction to < 2 drops - treatment period

End point title	Reduction in topical corticosteroids from entry dose: Time to reduction to < 2 drops - treatment period

End point description:

Reduction in topical corticosteroids from entry dose will be analysed for a subset of patients. Time to reduction to < 2 drops for those patients already on > = 2 drops at registration.

End point type	Secondary

End point timeframe:

Participants were assessed from registration up until:
- withdrawal
-time of 'no response'
- completion of treatment,
whichever came first

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: events				
Reduced drops	3			
censored	15			

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction in topical corticosteroids from entry dose: Time to reduction to 0 drops - treatment period

End point title	Reduction in topical corticosteroids from entry dose: Time to

	reduction to 0 drops - treatment period

End point description:

Reduction in topical corticosteroids from entry dose will be analysed from a subset of patients. Time to reduction to 0 drops for those patients already on > = 0 drops at registration.

End point type	Secondary

End point timeframe:

Participants were assessed from registration up until:
- withdrawal
-time of 'no response'
- completion of treatment,
whichever came first

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Events				
Reduced drops	3			
Censored	17			

Statistical analyses

No statistical analyses for this end point

Secondary: Total oral corticosteroid dose -treatment period and follow up

End point title	Total oral corticosteroid dose -treatment period and follow up

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 registration until the end of trial.

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	6[4]			
Units: mg standardised per year				
arithmetic mean (confidence interval 95%)	411.93 (374.01 to 453.69)			

Notes:

[4] - There were 21 patients registered and 6 received oral corticosteroids

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction in topical corticosteroids from entry dose: Time to reduction to < 2 drops - treatment period and follow up

End point title	Reduction in topical corticosteroids from entry dose: Time to reduction to < 2 drops - treatment period and follow up

End point description:

Reduction in in topical cortical corticosteroids from entry dose to < 2 drops will be analysed for a subset of patients. Time to reduction to < 2 drops for those patients already on > = 2 drop.

End point type	Secondary

End point timeframe:

Participants were assessed from registration until the end of trial.

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Events				
reduced drops	5			
censored	13			

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction in topical corticosteroids from entry dose: Time to reduction to 0 drops - treatment period and follow up

End point title	Reduction in topical corticosteroids from entry dose: Time to reduction to 0 drops - treatment period and follow up

End point description:

Reduction in corticosteroids from entry dose to 0 drops will be analysed for a subset of patients. Time to reduction to 0 drops for those patients already on > = 0 drops.

End point type	Secondary

End point timeframe:

Participants were assessed from registration until the end of trial.

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: events				
Reduced drops	4			
Censored	16			

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Statistical analyses have been added as a supplementary document

End point type	Secondary

End point timeframe:

Participants were assessed from registration up until:
- withdrawal
-time of 'no response'
- completion of treatment,
whichever came first

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	21[5]			
Units: score				
arithmetic mean (standard deviation)				
Best score: Baseline	0.07 (± 0.19)			
Best score: 4 weeks	0.04 (± 0.14)			
Best score: 8 weeks	0.03 (± 0.12)			
Best score: 12 weeks	-0.01 (± 0.17)			
Best score: 16 weeks	0.04 (± 0.08)			
Best score: 20 weeks	0.08 (± 0.06)			
Best score: 24 weeks	0.06 (± 0.11)			
Worst score: Baseline	0.17 (± 0.32)			
Worst score: 4 weeks	0.08 (± 0.17)			
Worst score: 8 weeks	0.14 (± 0.34)			
Worst score: 12 weeks	0.10 (± 0.31)			
Worst score: 16 weeks	0.06 (± 0.09)			
Worst score: 20 weeks	0.12 (± 0.09)			
Worst score: 24 weeks	0.11 (± 0.15)			

Notes:

[5] - 21 at baseline, 20 at 4 weeks, 19 at 8 weeks, 15 at 12 weeks, 6 at 16 weeks, 6 at 20 weeks, 4 at 24.

Attachments (see zip file)	joint modelling logmar.pdf

Statistical analyses

No statistical analyses for this end point

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

End point title	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.

No participants who had optic nerve were eligible in both eyes and therefore the analysis for resolution in both eyes was not possible.

End point type	Secondary

End point timeframe:

Participants were assessed from registration up until:
- withdrawal
-time of 'no response'
- completion of treatment,
whichever came first

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: subjects	2			

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

No participants who had macular oedema were eligible in both eyes and therefore the analysis for resolution in both eyes was not possible.

End point type	Secondary

End point timeframe:

Participants were assessed from registration up until:
- withdrawal
-time of 'no response'
- completion of treatment,
whichever came first

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: subjects	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Optic and Ocular: Number of participants with disease control at 12 weeks

End point title	Optic and Ocular: Number of participants with disease control at 12 weeks

End point description:

Disease control is defined as zero cells, with treatment for 12 weeks.

Two analyses were performed for this outcome: disease control in at least 1 eye, and disease control in both eyes.

End point type	Secondary

End point timeframe:

Assessed from registration until:
- time of no response
- completion of 6 months of treatment

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: subjects				
1 eye	0			
Both eyes	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Optic and Ocular: Number of participants with disease control at 24 weeks

End point title	Optic and Ocular: Number of participants with disease control at 24 weeks

End point description:

Disease control is defined as zero cells, with treatment for 24 weeks

Two analyses were performed for this outcome: disease control in at least 1 eye, and disease control in both eyes.

End point type	Secondary

End point timeframe:

Assessed from registration until:
- time of no response
- completion of 6 months of treatment

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: subjects				
1 eye	0			
Both eyes	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Optic and Ocular: Number of participants entering disease remission at 12 weeks

End point title	Optic and Ocular: Number of participants entering disease remission at 12 weeks

End point description:

Disease remission is defined as zero cells without treatment for 12 weeks.

Two analyses were performed for this outcome: disease remission in at least 1 eye, and disease remission in both eyes.

End point type	Secondary

End point timeframe:

Assessed from registration until:
- time of no response
- completion of 6 months of treatment

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: subjects				
1 eye	0			
Both eyes	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Optic and ocular: Number of participants entering disease remission at

24 weeks

End point title	Optic and ocular: Number of participants entering disease remission at 24 weeks

End point description:

Disease remission is defined as zero cells without treatment for 24 weeks.

two analyses were performed for this outcome: disease remission in at least 1 eye. and disease remission in both eyes.

End point type	Secondary

End point timeframe:

Participants were assessed from registration up until:
- withdrawal
-time of 'no response'
- completion of treatment,
whichever came first

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: subjects				
1 eye	0			
Both eyes	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Optic and Ocular: Duration of sustaining inactive disease

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

End point description:

Duration of sustaining inactive disease (zero cells, with or without topical treatment)

End point type	Secondary

End point timeframe:

Assessed from registration until:
- time of no response
- completion of 6 months of treatment

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: days				
arithmetic mean (confidence interval 95%)	2.66 (0 to 5.94)			

Statistical analyses

No statistical analyses for this end point

Secondary: Optic and ocular: Failure to reduce eye drops to 2 drops/day by or at 12 weeks

End point title	Optic and ocular: Failure to reduce eye drops to 2 drops/day by or at 12 weeks

End point description:

End point type	Secondary

End point timeframe:

Baseline to the 12 weeks visit

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: subjects	9			

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

The CHQ consists of two scores:
Physical score (PhS)
Psychosocial score (PsS)

Statistical analyses have been added as a supplementary document

End point type	Secondary

End point timeframe:

Participants were assessed from registration up until:
- withdrawal
-time of 'no response'
- completion of treatment,
whichever came first

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	20[6]			
Units: assessment score				
arithmetic mean (standard deviation)				
PhS: Baseline	39.55 (± 17.72)			
PhS: 4 weeks	45.64 (± 12.03)			
PhS: 8 weeks	44.47 (± 13.38)			
PhS: 12 weeks	40.96 (± 17.55)			
PhS: 16 weeks	41.61 (± 14.43)			
PhS: 20 weeks	42.12 (± 13.87)			
PhS: 24 weeks	45.21 (± 12.12)			
PsS: Baseline	51.50 (± 13.54)			
PsS: 4 weeks	54.03 (± 10.67)			
PsS: 8 weeks	54.95 (± 7.24)			
PsS: 12 weeks	53.13 (± 10.46)			
PsS: 16 weeks	53.35 (± 11.76)			
PsS: 20 weeks	55.66 (± 5.23)			
PsS: 24 weeks	50.77 (± 10.69)			

Notes:

[6] - 20 at baseline & 4 weeks, 18 at 8, 4 at 12, 6 at 16, 6 at 20, 4 at 24.

Attachments (see zip file)	chq/chq.pdf

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Statistical analyses have been added as a supplementary document

End point type	Secondary

End point timeframe:

Participants were assessed from registration up until:
- withdrawal
-time of 'no response'
- completion of treatment,

whichever came first

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	21[7]			
Units: assessment score				
arithmetic mean (standard deviation)				
Baseline	0.37 (± 0.58)			
4 weeks	0.30 (± 0.54)			
8 weeks	0.48 (± 0.71)			
12 weeks	0.51 (± 0.80)			
16 weeks	0.23 (± 0.37)			
20 weeks	0.25 (± 0.40)			
24 weeks	0.31 (± 0.41)			

Notes:

[7] - 21 at baseline & 4 weeks, 19 at 8, 15 at 12, 6 at 16, 6 at 20, 4 at 24

Attachments (see zip file)	Childhood Health Assessment Questionnaire.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: American College of Rheaumatology (ACR) score

End point title	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.

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.

Statistical analyses have been added as a supplementary document.

End point type	Secondary

End point timeframe:

Participants were assessed from registration up until:
- withdrawal
-time of 'no response'
- completion of treatment,
whichever came first

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	21[8]			
Units: ACR frequency				
number (not applicable)				
4 weeks: ACR30	6			
4 weeks: ACR50	5			
4 weeks: ACR70	2			
4 weeks: ACR90	1			
4 weeks: ACR100	0			
8 weeks: ACR30	7			
8 weeks: ACR50	6			
8 weeks: ACR70	3			
8 weeks: ACR90	0			
8 weeks: ACR100	0			
12 weeks: ACR30	5			
12 weeks: ACR50	4			
12 weeks: ACR70	4			
12 weeks: ACR90	1			
12 weeks: ACR100	1			
16 weeks: ACR30	3			
16 weeks: ACR50	3			
16 weeks: ACR70	2			
16 weeks: ACR90	1			
16 weeks: ACR100	0			
20 weeks: ACR30	3			
20 weeks: ACR50	3			
20 weeks: ACR70	2			
20 weeks: ACR 90	2			
20 weeks: ACR100	2			
24 weeks: ACR30	2			
24 weeks: ACR50	2			
24 weeks: ACR70	1			
24 weeks: ACR90	1			
24 weeks: ACR100	0			

Notes:

[8] - See supplementary table for the number of patients who had missing data

Attachments (see zip file)	ACR.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants requiring change in biologic /disease-modifying anti-rheumatic drugs (DMARDS) therapy due to disease flare of their arthritis or failure to response to treatment of arthritis

End point title	Number of participants requiring change in biologic /disease-modifying anti-rheumatic drugs (DMARDS) therapy due to disease flare of their arthritis or failure to response to treatment of arthritis

End point description:

DMARDs are disease-modifying anti-rheumatic drugs.

End point type	Secondary

End point timeframe:

Participants were assessed from registration up until:
- withdrawal
-time of 'no response'
- completion of treatment,
whichever came first

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: subjects	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants undergoing flare of arthritis

End point title	Number of participants undergoing flare of arthritis

End point description:

The definition of 'disease flare' is a worsening of 30% 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:

Assessed from registration until:
- time of no response
- completion of 6 months of treatment

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: subjects				
Disease flare	0			
No disease flare	21			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants in remission on and off medication of their JIA

End point title	Number of participants in remission on and off medication of their JIA

End point description:

Clinical remission of JIA whilst on medication is defined as per Wallace (2004):
- The criteria for inactive disease must be met for a minimum of 6 continuous months while the patient is on (anti-rheumatic, anti-inflammatory* and anti-uveitis) medication in order for the patient to be considered to be in a state of clinical remission on medication.

Clinical remission of JIA whilst off medication is defined as per Wallace (2004):
- The criteria for inactive disease (see definition in section 17.4.9.2 above) must be met for a minimum of 12 continuous months while off all anti-rheumatic, anti-inflammatory* and anti-uveitis medications in order for the patient to be considered to be in a state of clinical remission off medication.

Patients will not be able to assessed for inactive disease for a minimum of 12 months with the treatment phase being 6 months and the follow-up phase being 1 month so clinical remission of JIA whilst off medication is unable to be analysed.

End point type	Secondary

End point timeframe:

Throughout the duration of the study

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: subjects				
Achieved Clinical remission on medication	0			
Not achieved clinical remission on medication	21			

Statistical analyses

No statistical analyses for this end point

Secondary: Juvenile Arthritis Disease Activity Score (JADAS)

End point title	Juvenile Arthritis Disease Activity Score (JADAS)

End point description:

The Juvenile Arthritis Disease Activity Score (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 from its four components detailed below, giving global scores of 0-57, 0-101 and 0-40 for the JADAS-27, JADAS-71 and JADAS-10 respectively.

Statistical analyses have been added as a supplementary document

End point type	Secondary

End point timeframe:

Participants were assessed from registration up until:

- withdrawal
-time of 'no response'
- completion of treatment,
whichever came first

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: JADAS				
arithmetic mean (standard deviation)				
JADAS10: Baseline	5.78 (± 5.21)			
JADAS10: Visit 1	2.62 (± 3.64)			
JADAS10: Visit 2	3.04 (± 2.86)			
JADAS10: Visit 3	4.79 (± 3.98)			
JADAS10: Visit 4	2.88 (± 4.23)			
JADAS10: Visit 5	3.27 (± 3.46)			
JADAS10: Visit 6	3.11 (± 4.78)			
JADAS27: Baseline	5.58 (± 5.04)			
JADAS27: Visit 1	2.46 (± 3.3)			
JADAS27: Visit 2	3.04 (± 2.86)			
JADAS27: Visit 3	4.79 (± 3.98)			
JADAS27: Visit 4	2.88 (± 4.23)			
JADAS27: Visit 5	3.07 (± 3.49)			
JADAS27: Visit 6	3.11 (± 4.78)			
JADAS71: Baseline	5.78 (± 5.21)			
JADAS71: Visit 1	2.62 (± 3.64)			
JADAS71: Visit 2	3.04 (± 2.86)			
JADAS71: Visit 3	4.79 (± 3.98)			
JADAS71: Visit 4	2.88 (± 4.23)			
JADAS71: Visit 5	3.27 (± 3.46)			
JADAS71: Visit 6	3.11 (± 4.78)			

Attachments (see zip file)	Juvenile Arthritis Disease Activity Score/Juvenile Arthritis

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameters

End point title	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
-LDL
-HDL
-Triglycerides
-Total cholesterol
-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:

Throughout the duration of the study.

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: See supplementary tables	21			

Attachments (see zip file)	Laboratory Parameters/Laboratory parameters.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Compliance according to participnat diaries

End point title	Compliance according to participnat diaries

End point description:

Treatment diaries were used to estimate participant compliance. No formal statistical analysis was

undertaken.

End point type	Secondary

End point timeframe:

Participants were assessed from registration up until:
- withdrawal
-time of 'no response'
- completion of treatment,
whichever came first

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: percent				
Compliance	92			

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction in systemic corticosteroid dose from entry dose to 0mg - treatment period

End point title	Reduction in systemic corticosteroid dose from entry dose to 0mg - treatment period

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 registration.

End point type	Secondary

End point timeframe:

Participants were assessed from registration up until:
- withdrawal
-time of 'no response'
- completion of treatment,
whichever came first

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: Events				
Reduced dose	0			
censored	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction in systemic corticosteroid dose from entry dose to <5mg - treatment period

End point title	Reduction in systemic corticosteroid dose from entry dose to <5mg - treatment period

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 registration.

End point type	Secondary

End point timeframe:

Participants were assessed from registration up until:
- withdrawal
-time of 'no response'
- completion of treatment,
whichever came first

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: events				
Event	0			
Censored	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of systemic corticosteroid dose from entry dose - treatment period

End point title	Rate of systemic corticosteroid dose from entry dose - treatment period

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 registration up until:
- withdrawal
-time of 'no response'
- completion of treatment,
whichever came first

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: mg (standardised to per patinet year)				
arithmetic mean (confidence interval 95%)	295.29 (263.46 to 330.97)			

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction in systemic corticosteroid dose from entry dose to 0mg - treatment period and follow up

End point title	Reduction in systemic corticosteroid dose from entry dose to 0mg - treatment period and follow up

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 registration.

End point type	Secondary

End point timeframe:

From registration until the end of study.

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: events				
Event	0			
Censored	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction in systemic corticosteroid dose from entry dose to <5mg - treatment period and follow up

End point title	Reduction in systemic corticosteroid dose from entry dose to <5mg - treatment period and follow up

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 registration.

End point type	Secondary

End point timeframe:

Participants were assessed from registration up until:
- withdrawal

-time of 'no response'
- completion of treatment,
whichever came first

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Events				
Event	0			
Censored	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of systemic corticosteroid dose from entry dose - treatment period

End point title	Rate of systemic corticosteroid dose from entry dose - treatment period

End point description:

End point type	Secondary

End point timeframe:

Participants were assessed from registration up until:
- withdrawal
-time of 'no response'
- completion of treatment,
whichever came first

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: mg (standardised to per patient year)				
arithmetic mean (confidence interval 95%)	411.93 (374.01 to 453.69)			

Statistical analyses

No statistical analyses for this end point

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	Tocilizumab

Reporting group description: -

Serious adverse events	Tocilizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 21 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

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

Non-serious adverse events	Tocilizumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 21 (42.86%)		
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
General disorders and administration site conditions			
Complication associated with device			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Injection site bruising			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Injection site reaction			

subjects affected / exposed	8 / 21 (38.10%)		
occurrences (all)	24		
Pyrexia			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Seasonal allergy			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	5		
Hypomenorrhoea			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Menorrhagia			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	5 / 21 (23.81%)		
occurrences (all)	7		
Nasal congestion			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	6 / 21 (28.57%)		
occurrences (all)	7		
Wheezing			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	2		
Investigations			

Alanine aminotransferase increased				
subjects affected / exposed	3 / 21 (14.29%)			
occurrences (all)	4			
Aspartate aminotransferase increased				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences (all)	1			
Blood bilirubin increased				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences (all)	1			
Blood calcium decreased				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences (all)	1			
Blood cholesterol increased				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences (all)	1			
Blood triglycerides increased				
subjects affected / exposed	3 / 21 (14.29%)			
occurrences (all)	3			
High density lipoprotein decreased				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences (all)	1			
Intraocular pressure increased				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences (all)	4			
Low density lipoprotein increased				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences (all)	1			
Neutrophil count				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences (all)	1			
Neutrophil count decreased				
subjects affected / exposed	3 / 21 (14.29%)			
occurrences (all)	4			
Red blood cell sedimentation rate increased				

subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
White blood cell count decreased			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Ligament sprain			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Suture related complication			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Wound			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Congenital, familial and genetic disorders			
Syringomyelia			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	5 / 21 (23.81%)		
occurrences (all)	8		
Syncope			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Increased tendency to bruise			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		

Lymphadenopathy			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Neutropenia			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	3		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	2		
Eye disorders			
Eyelid oedema			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Ocular hyperaemia			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Uveitis			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	3		
Vision blurred			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	3		
Visual acuity reduced			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Constipation			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Gastrooesophageal reflux disease			

subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
Mouth ulceration subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 4		
Oral pain subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
Toothache subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
Vomiting subjects affected / exposed occurrences (all)	3 / 21 (14.29%) 3		
Skin and subcutaneous tissue disorders			
Acne subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
Eczema subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
Erythema subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
Rash subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
Skin burning sensation subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	4 / 21 (19.05%) 8		
Back pain			

subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	3		
Joint range of motion decreased			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Joint swelling			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Juvenile idiopathic arthritis			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Scoliosis			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Temporomandibular joint syndrome			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Tenosynovitis			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Cystitis			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Ear infection			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Molluscum contagiosum			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	3		

Oral herpes			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Otitis externa			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Paronychia			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	4		
Skin infection			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Tonsillitis			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Tooth abscess			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	3		
Urinary tract infection			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Vulvovaginal candidiasis			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Wound infection			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 August 2015	The first amendment to the protocol updated the number of centres to 6 and corrected the schematic of study design to show that patients who respond to treatment at 3 months complete the treatment period and do not cease trial treatment at 12 week. ILAR diagnostic criteria from inclusion criteria 1 was merged with exclusion criteria 1. Clarification of definition of active anterior uveitis added to inclusion criteria 2 and inclusion criteria's 4 and 5 merged into one criteria. Previous registration added as an exclusion, exclusion criteria updated to state that patients on oral anti-glaucoma therapy are excluded, clarification added to exclusion criteria stating that patients need to be on stable eye drops for 1 week prior to screening, untreated latent TB criteria from exclusion 14 added to exclusion 15, exclusion criteria 29 removed as it is covered in exclusion criteria 28 (immunization with live/attenuated vaccine) and exclusion criteria added excluded patient who have had joint injections with 4 weeks prior to registration. Method of registering patients amended to instruct sites to register patients via an online registration system. References to SmPC replace with IB. Text added stating that patients who have an increase in weight over 30kg or decrease in weight to less than 30kg should switch dosing regimen, text added giving guidance for interrupting trial treatment and text added giving guidance on discontinuing trial treatment. Text added to confirm that patients should receive trial injections up to and including week 24, medications permitted updated to confirm that patients need to be on stable dose of eye drops 1 week prior to screening, and medications not permitted updated to include Systemic treatment with acetazolamide is not allowed.
28 August 2015	(Continued) Table of assessment updated to clarify which assessments are done at screening and which are done at registration. Information added confirming that interim analysis is carried out after 10 patients have been recruited. Adverse event of special interest list updated in line with AESI guidance from Roche and appendix added giving guidance for liver function tests.
05 November 2015	The second amendment updated trial management and monitoring details, added a secondary outcome to develop a fully consented trial related Bio bank for subsequent investigation and an amendment to minimum time needed between visits to assessing response to trial treatment.
11 January 2016	The third amendment to the protocol updated the OCT section to that macular foveal thicknes results will be collected.
14 July 2016	The fourth amendment to the protocol added JADAS as a secondary endpoint. Text added instructing sites to contact trial co-ordinator for any queries relating to reduction of MTX. Text added to state that ANA, dsDNA and ENA test should be conducted if patients stop treatment or withdraw before week 24. Text added to state that ANA, dsDNA and ENA test should be conducted if patients stop treatment or withdraw before 24. Text amended to reflect that local investigators assess relationship and seriousness of adverse events only. Contact details for reporting serious adverse events updated.

31 May 2017	The fifth amendment to the protocol updated trial telephone and fax details. White blood cell (WBC) count criteria amended to 4,000/mm3 (<4.0 x 109/L), platelet count added in 10^9/L to correspond with CRFs and neutrophil count amended to <2,000/mm3 (<2.0 x 109/L). Text were added to state that full eligibility must be confirmed by a doctor on the delegation log and to state that a patient may only be registered once full eligibility has been confirmed. Total Bilirubinin µmol added to correspond with CRF, as well as, neutrophil count in x10^9/L, and platelet count in x10^9/L. Guidance adding for discontinuing treatment for the trial and non-trial eye, medication allowed in the non-trial eye, and medication not allowed in the non-trial eye. Fax number for reporting SAEs updated and clarification to time point for reporting SAEs.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported