Clinical trial results:
A phase II randomised placebo controlled double blinded trial of Interleukin 1 blockade in Acute Severe Colitis

Summary

EudraCT number	2017-001389-10
Trial protocol	GB
Global end of trial date	24 September 2021

Results information

Result version number	v1 (current)
This version publication date	11 October 2022
First version publication date	11 October 2022
Summary attachment (see zip file)	IASO Protocol Version 3.0 dated 30Oct18 (IASO protocol v3.0 301018 (Clean).pdf)

Trial information

Trial identification

Sponsor protocol code	IASO CCTU-0165 RG81897

Additional study identifiers

ISRCTN number	ISRCTN43717130
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	IRAS: 201505, REC Reference: 17/EE/0347, NIHR Project: EME Ref: 14/201/02

Notes:

Sponsors

Sponsor organisation name	Cambridge University Hospitals NHS Foundation Trust
Sponsor organisation address	Box 401, Cambridge Clinical Trials Unit Level 6, Coton House, Cambridge, United Kingdom, CB20QQ
Public contact	Carrie Bayliss, Cambridge Clinical Trials Unit, +44 (0)1223 348158, cctu@addenbrookes.nhs.uk
Scientific contact	Carrie Bayliss, Cambridge Clinical Trials Unit, +44 (0)1223 348158, cctu@addenbrookes.nhs.uk
Sponsor organisation name	Cambridge University Hospitals NHS Foundation Trust
Sponsor organisation address	Box 277, Addenbrooke's Hospital, Cambridge, United Kingdom, Cambridge, United Kingdom, CB20QQ
Public contact	Steven Kelleher, +44 (0)1223 217418, research@addenbrookes.nhs.uk, CUH NHS Foundation Trust and the University of Cambridge, +44 (0)1223 217418, research@addenbrookes.nhs.uk
Scientific contact	Steven Kelleher, +44 (0)1223 217418, research@addenbrookes.nhs.uk, CUH NHS Foundation Trust and the University of Cambridge, +44 (0)1223 217418, research@addenbrookes.nhs.uk

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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 May 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 March 2021
Global end of trial reached?	Yes
Global end of trial date	24 September 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The aim of this trial is to compare the clinical effects of anakinra with placebo when given in addition to current standard care in patients with acute severe ulcerative colitis.

The primary measure of success will be any difference in the proportion of participants in the group receiving anakinra who needed escalation to more intensive medical or surgical therapy (known as rescue therapy) by 10 days after standard treatment was started, when compared with the group of participants receiving placebo.

Protection of trial subjects:

The TSC (Trial Steering Committee) provided overall supervision with respect to the conduct of the study. Dr Oliver Brain was the independent chairman.

The ethical and safety aspects of the trial were overseen by an independent DMC which was chaired by Dr Peter Irving. DMC meetings were timed so that reports could be fed into the TSC meetings.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 November 2017
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: 113
Worldwide total number of subjects	113
EEA total number of subjects	0

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)	0
Adolescents (12-17 years)	1
Adults (18-64 years)	106
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Initially 214 patients from approximately 20 UK NHS acute hospitals were planned to be recruited. However, due to futility of analysis after 100 patients had been recruited, the trial was terminated early, resulting in a total of 113 patients being recruited and analysed from May 2018 to February 2021.

Pre-assignment

Screening details:

125 patients were assessed for eligibility. 12 people failed screening due to MTWSI score being too low, not ASUC, diagnosed endoscopy, did not meet the inclusion criteria, oral steroid less than 8 weeks ago, withdrew consent, and concurrent biologic. 113 patients were randomised.

Pre-assignment period milestones

Number of subjects started	125[1]
Number of subjects completed	113

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 1
Reason: Number of subjects	MTWSI too low: 6
Reason: Number of subjects	Not ASUC: 1
Reason: Number of subjects	Diagnosed endoscopy: 1
Reason: Number of subjects	Did not meet inclusion criteria: 1
Reason: Number of subjects	Oral steroid less than 8 weeks ago: 1
Reason: Number of subjects	Concurrent biologic: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 125 patients were assessed for eligibility. However, due to the reasons stated, 12 failed screening, resulting in the 113 patients randomised and analysed. This is the worldwide number enrolled in the trial.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

The placebo group will receive an injection with the same physical appearance as Anakinra to preserve blinding. They will also receive current standard of care.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details:

Same physical appearance as the IMP. Given the same as the IMP.

Arm title	Anakinra

Arm description:

Anakinra is a clear, colourless to white solution for injection which may contain some translucent-to-white particles of protein in the solution. Current standard of care will also be given.

Arm type	Experimental
Investigational medicinal product name	Anakinra
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details:

Initial IV dose will be 100mg, and then subsequent SC dose will be 100mg for up to 10 doses as per administration schedule.

Number of subjects in period 1	Placebo	Anakinra
Started	55	58
Completed	55	58

Period 2

Period 2 title	Day 10
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

The placebo group will receive an injection with the same physical appearance as Anakinra to preserve blinding. They will also receive current standard of care.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details:

Same physical appearance as the IMP. Given the same as the IMP.

Arm title	Anakinra

Arm description:

Anakinra is a clear, colourless to white solution for injection which may contain some translucent-to-white particles of protein in the solution. Current standard of care will also be given.

Arm type	Experimental
Investigational medicinal product name	Anakinra
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details:

Initial IV dose will be 100mg, and then subsequent SC dose will be 100mg for up to 10 doses as per administration schedule.

Number of subjects in period 2	Placebo	Anakinra
Started	55	58
Completed	51	55
Not completed	4	3
Consent withdrawn by subject	4	2
Physician decision	-	1

Period 3

Period 3 title	Day 98
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

The placebo group will receive an injection with the same physical appearance as Anakinra to preserve blinding. They will also receive current standard of care.

Arm type	Placebo

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

Dosage and administration details:

Same physical appearance as the IMP. Given the same as the IMP.

Arm title	Anakinra

Arm description:

Anakinra is a clear, colourless to white solution for injection which may contain some translucent-to-white particles of protein in the solution. Current standard of care will also be given.

Arm type	Experimental
Investigational medicinal product name	Anakinra
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details:

Initial IV dose will be 100mg, and then subsequent SC dose will be 100mg for up to 10 doses as per administration schedule.

Number of subjects in period 3	Placebo	Anakinra
Started	51	55
Completed	51	54
Not completed	0	1
Physician decision	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
The placebo group will receive an injection with the same physical appearance as Anakinra to preserve blinding. They will also receive current standard of care.	
Reporting group title	Anakinra
Reporting group description:	
Anakinra is a clear, colourless to white solution for injection which may contain some translucent-to-white particles of protein in the solution. Current standard of care will also be given.	

Reporting group values	Placebo	Anakinra	Total
Number of subjects	55	58	113
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Created this variable by subtracting the birth date from the randomisation date. This is the age at randomisation.			
Units: years			
arithmetic mean	38.6	39.5	
standard deviation	± 14.2	± 15.1	-
Gender categorical			
Female or male			
Units: Subjects			
Female	25	21	46
Male	30	37	67
Therapy with immunomodulators or oral Janus kinase inhibitors			
This was a stratification factor.			
Units: Subjects			
Yes	16	18	34
No	39	40	79
Oral corticosteroids within 8 weeks prior to first dose of IV corticosteroids			
A stratification factor.			
Units: Subjects			
Yes	21	24	45
No	34	34	68
Current smoker			

Asked if they currently smoked.			
Units: Subjects			
Yes	6	8	14
No	49	50	99
Endoscopic MAYO score			
Where available			
Units: Subjects			
One	5	2	7
Two	12	16	28
Three	13	16	29
Not available	25	24	49
EQ5D: VAS score			
Baseline score summary of the EQ5D pain score.			
Units: unknown			
arithmetic mean	46.4	44.3	
standard deviation	± 19.2	± 19.7	-
EQ5D: Utility score			
Baseline EQ5D score of utility.			
Units: unknown			
arithmetic mean	0.588	0.561	
standard deviation	± 0.209	± 0.228	-
MTWSI score			
Modified Truelove Witts severity index score at baseline.			
Units: unknown			
arithmetic mean	14	14.3	
standard deviation	± 2.25	± 2.24	-
CUCQ-32 score			
CUCQ-32 is a questionnaire. This is the baseline summary score.			
Units: unknown			
arithmetic mean	164	162	
standard deviation	± 40.3	± 43.5	-
Duration of disease prior to randomisation			
Units: year			
arithmetic mean	5.78	5.83	
standard deviation	± 7.16	± 7.83	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
The placebo group will receive an injection with the same physical appearance as Anakinra to preserve blinding. They will also receive current standard of care.	
Reporting group title	Anakinra
Reporting group description:	
Anakinra is a clear, colourless to white solution for injection which may contain some translucent-to-white particles of protein in the solution. Current standard of care will also be given.	
Reporting group title	Placebo
Reporting group description:	
The placebo group will receive an injection with the same physical appearance as Anakinra to preserve blinding. They will also receive current standard of care.	
Reporting group title	Anakinra
Reporting group description:	
Anakinra is a clear, colourless to white solution for injection which may contain some translucent-to-white particles of protein in the solution. Current standard of care will also be given.	
Reporting group title	Placebo
Reporting group description:	
The placebo group will receive an injection with the same physical appearance as Anakinra to preserve blinding. They will also receive current standard of care.	
Reporting group title	Anakinra
Reporting group description:	
Anakinra is a clear, colourless to white solution for injection which may contain some translucent-to-white particles of protein in the solution. Current standard of care will also be given.	

Primary: Need for rescue therapy or colectomy

End point title	Need for rescue therapy or colectomy
End point description:	
If day 10 assessments were performed, the variable would be yes if the time difference between rescue therapy and first IV corticosteroid is <10 days and they answered yes to having had medical or surgical rescue therapy. The variable would be "no" if they did not have medical or surgical rescue therapy or the time difference was >10 days. If no day 10 assessment was performed, the endpoint was missing.	
End point type	Primary
End point timeframe:	
The endpoint is need for rescue therapy or colectomy up to day 10.	

End point values	Placebo	Anakinra		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	54		
Units: People				
Yes	13	23		
No	37	31		

Statistical analyses

Statistical analysis title	Logistic regression model 1

Statistical analysis description:

The absolute risk difference will be estimated for the incidence rate of the need for medical or surgical rescue therapy within 10 days between the treatment arms. 3 separate logistic regression models will be fit. One without stratification factors. One adjusting for stratification factors, and one with the stratification factors and prior diagnosis of IBD.

Comparison groups	Placebo v Anakinra
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	0.166
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.016
upper limit	0.341

Statistical analysis title	Logistic regression model 2

Statistical analysis description:

The absolute risk difference will be estimated for the incidence rate of the need for medical or surgical rescue therapy within 10 days between the treatment arms. 3 separate logistic regression models will be fit. Model 1 without stratification factors. Model 2 adjusting for stratification factors, and model 3 with the stratification factors and prior diagnosis of IBD.

Comparison groups	Placebo v Anakinra
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.008
upper limit	0.339

Statistical analysis title	Logistic regression model 3

Statistical analysis description:

The absolute risk difference will be estimated for the incidence rate of the need for medical or surgical rescue therapy within 10 days between the treatment arms. 3 separate logistic regression models will be

fit. Model 1 without stratification factors. Model 2 adjusting for stratification factors, and model 3 with the stratification factors and prior diagnosis of IBD.

Comparison groups	Placebo v Anakinra
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	0.143
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.041
upper limit	0.324

Secondary: Colectomy within 98 days

End point title	Colectomy within 98 days

End point description:

If day 98 assessment was performed, the variable was "yes" if colectomy was performed and the time difference was <98 days. The variable was "no" if colectomy was not performed or the time difference was >98 days. If no day 98 assessment was performed, the value would be missing.

End point type	Secondary

End point timeframe:

98 days following first IV corticosteroid.

End point values	Placebo	Anakinra		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	54		
Units: People				
Yes	2	6		
No	48	48		

Statistical analyses

Statistical analysis title	Logistic regression model 1

Statistical analysis description:

The incidence of colectomy will be compared in a logistic regression model to estimate the effect of treatment with anakinra. The log odds ratio will be estimated. Model 1 contains only treatment arm, and model 2 contains the stratification factors as well.

Comparison groups	Placebo v Anakinra

Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Log odds ratio
Point estimate	1.099
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.425
upper limit	3.053

Statistical analysis title	Logistic regression model 2

Statistical analysis description:

The incidence of colectomy will be compared in a logistic regression model to estimate the effect of treatment with anakinra. The log odds ratio will be estimated. Model 1 contains only treatment arm, and model 2 contains the stratification factors as well.

Comparison groups	Placebo v Anakinra
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Log odds ratio
Point estimate	1.106
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.432
upper limit	3.07

Secondary: Time to clinical response

End point title	Time to clinical response

End point description:

Time to clinical response is date from the first IV corticosteroid to clinical response.
Events: patients who had two consecutive days with MTWSI<10 without missing any assessments prior to the event; the date of first assessment of these two consecutive days will be used in the time to clinical response.
Censoring: date of the last consecutive assessment day 0.5 if day 1 assessment was missing; patients who had two consecutive days with MTWSI<10 but with missing assessment before will be censored at the last consecutive assessment.

End point type	Secondary

End point timeframe:

Date of first MTWSI assessment or last consecutive assessment.

End point values	Placebo	Anakinra		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	57		
Units: day				
number (not applicable)	53	57		

Attachments (see zip file)	Kaplan-Meier curve/fig_6.14.png

Statistical analyses

Statistical analysis title	Cox model

Statistical analysis description:

Cox model for the time to clinical response containing the stratification factors and treatment group. The result for treatment group will be given.

Comparison groups	Placebo v Anakinra
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.27 [1]
Method	Regression, Cox
Parameter estimate	Log hazard ratio
Point estimate	0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	0.77
Variability estimate	Standard error of the mean
Dispersion value	0.25

Notes:

[1] - For no therapy with immunomodulators, the p-value was 0.73, and for no oral corticosteroids, the p-value was 0.45

Secondary: Time to medical or surgical rescue therapy

End point title	Time to medical or surgical rescue therapy

End point description:

Time to medical or surgical rescue therapy, measured according to the time after the first dose of IV corticosteroids until the time that rescue therapy occurs (using definitions as set out in primary endpoint). Data will be captured up to the same time point as the primary endpoint.

End point type	Secondary

End point timeframe:

Data will be captured up to day 10 assessment.

End point values	Placebo	Anakinra		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	54		
Units: day				
number (not applicable)	50	54		

Attachments (see zip file)	Kaplan-Meier curve/fig_6.16.png

Statistical analyses

Statistical analysis title	Cox model

Statistical analysis description:

For time to medical or surgical rescue therapy. The model contains the two stratification factors and treatment group. The estimate for treatment group will be presented.

Comparison groups	Placebo v Anakinra
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.17 [2]
Method	Regression, Cox
Parameter estimate	Log hazard ratio
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	1.13
Variability estimate	Standard error of the mean
Dispersion value	0.34

Notes:

[2] - For no therapy, the p-value was 0.16. For no oral corticosteroids, the p-value was 0.19.

Secondary: Burden of MTWSI

End point title	Burden of MTWSI

End point description:

End point type	Secondary

End point timeframe:

The average MTWSI was assessed in a mixed model. This was meaured from baseline to day 5.

End point values	Placebo	Anakinra		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	57		
Units: unit(s)				
number (not applicable)	52	57		

Statistical analyses

Statistical analysis title	Random effects mixed model

Statistical analysis description:

To test the burden of MTWSI, a random effects mixed model for repeated measurements will be fitted. The fixed effects will include treatment allocation, baseline MTWSI, time of assessments (days 1-5), and an interaction between treatment allocation and time. The dependent variable will be the total MTWSI score repeated from days 1 to 5. A random intercept will be fitted to allow the average MTWSI score to be higher or lower for each individual.

Comparison groups	Placebo v Anakinra
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.83
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.45
upper limit	1.17
Variability estimate	Standard error of the mean
Dispersion value	0.67

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Day 10. Expected AEs or SAEs as follows did not require expedited reporting:
- Diarrhoea/worsening diarrhoea
- Abdominal pain/increased abdominal pain
- Rectal pain/worsening rectal pain
- Development of toxic megacolon or hypoalbuminaemia

Adverse event reporting additional description:

Reportable SAEs/SARs were defined as any untoward medical occurrence that at any dose:
- Results in death
- Is life-threatening
- Requires hospitalisation or prolongation of inpatients´ hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Anakinra
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Anakinra	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 58 (15.52%)	10 / 55 (18.18%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
HEADACHE	Additional description: HEADACHE		
subjects affected / exposed	1 / 58 (1.72%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PARAESTHESIA	Additional description: PARAESTHESIA		
subjects affected / exposed	1 / 58 (1.72%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERONEAL NERVE PALSY	Additional description: PERONEAL NERVE PALSY		

subjects affected / exposed	1 / 58 (1.72%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
CHOLANGITIS SCLEROSING	Additional description: CHOLANGITIS SCLEROSING		
subjects affected / exposed	0 / 58 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
COLITIS ULCERATIVE	Additional description: COLITIS ULCERATIVE		
subjects affected / exposed	7 / 58 (12.07%)	7 / 55 (12.73%)	
occurrences causally related to treatment / all	2 / 7	5 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONSTIPATION	Additional description: CONSTIPATION		
subjects affected / exposed	1 / 58 (1.72%)	0 / 55 (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			
CLOSTRIDIUM DIFFICILE INFECTION	Additional description: CLOSTRIDIUM DIFFICILE INFECTION		
subjects affected / exposed	0 / 58 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA	Additional description: PNEUMONIA		
subjects affected / exposed	0 / 58 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Anakinra	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 58 (22.41%)	19 / 55 (34.55%)	
Investigations			
BLOOD POTASSIUM DECREASED	Additional description: BLOOD POTASSIUM DECREASED		

subjects affected / exposed	2 / 58 (3.45%)	2 / 55 (3.64%)	
occurrences (all)	2	2	
LIVER FUNCTION TEST ABNORMAL	Additional description: LIVER FUNCTION TEST ABNORMAL		
subjects affected / exposed	2 / 58 (3.45%)	1 / 55 (1.82%)	
occurrences (all)	2	1	
Cardiac disorders			
ATRIAL FIBRILLATION	Additional description: ATRIAL FIBRILLATION		
subjects affected / exposed	0 / 58 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
Nervous system disorders			
HEADACHE	Additional description: HEADACHE		
subjects affected / exposed	0 / 58 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
NEUROPATHY PERIPHERAL	Additional description: NEUROPATHY PERIPHERAL		
subjects affected / exposed	1 / 58 (1.72%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
PRESYNCOPE	Additional description: PRESYNCOPE		
subjects affected / exposed	1 / 58 (1.72%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
CHEST PAIN	Additional description: CHEST PAIN		
subjects affected / exposed	0 / 58 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
NIGHT SWEATS	Additional description: NIGHT SWEATS		
subjects affected / exposed	0 / 58 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
PERIPHERAL SWELLING	Additional description: PERIPHERAL SWELLING		
subjects affected / exposed	1 / 58 (1.72%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
PYREXIA	Additional description: PYREXIA		
subjects affected / exposed	0 / 58 (0.00%)	3 / 55 (5.45%)	
occurrences (all)	0	5	
Gastrointestinal disorders			
ABDOMINAL DISTENSION	Additional description: ABDOMINAL DISTENSION		
subjects affected / exposed	0 / 58 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	

ABDOMINAL PAIN	Additional description: ABDOMINAL PAIN		
subjects affected / exposed	0 / 58 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
COLITIS ULCERATIVE	Additional description: COLITIS ULCERATIVE		
subjects affected / exposed	0 / 58 (0.00%)	3 / 55 (5.45%)	
occurrences (all)	0	3	
CONSTIPATION	Additional description: CONSTIPATION		
subjects affected / exposed	1 / 58 (1.72%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
DYSPEPSIA	Additional description: DYSPEPSIA		
subjects affected / exposed	0 / 58 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
GASTRITIS	Additional description: GASTRITIS		
subjects affected / exposed	0 / 58 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
LOWER ABDOMINAL PAIN	Additional description: LOWER ABDOMINAL PAIN		
subjects affected / exposed	0 / 58 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
NAUSEA	Additional description: NAUSEA		
subjects affected / exposed	0 / 58 (0.00%)	2 / 55 (3.64%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
COUGH	Additional description: COUGH		
subjects affected / exposed	0 / 58 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
OOROPHARYNGEAL PAIN	Additional description: OOROPHARYNGEAL PAIN		
subjects affected / exposed	0 / 58 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
HYPERHIDROSIS	Additional description: HYPERHIDROSIS		
subjects affected / exposed	1 / 58 (1.72%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
RASH	Additional description: RASH		
subjects affected / exposed	1 / 58 (1.72%)	3 / 55 (5.45%)	
occurrences (all)	1	3	
Psychiatric disorders			

ANXIETY	Additional description: ANXIETY		
subjects affected / exposed	0 / 58 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
PSYCHOGENIC SEIZURE	Additional description: PSYCHOGENIC SEIZURE		
subjects affected / exposed	0 / 58 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
BACK PAIN	Additional description: BACK PAIN		
subjects affected / exposed	2 / 58 (3.45%)	1 / 55 (1.82%)	
occurrences (all)	2	1	
JOINT SWELLING	Additional description: JOINT SWELLING		
subjects affected / exposed	0 / 58 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
MUSCULSKELETAL PAIN	Additional description: MUSCULSKELETAL PAIN		
subjects affected / exposed	0 / 58 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	2	
PAIN IN EXTREMITY	Additional description: PAIN IN EXTREMITY		
subjects affected / exposed	1 / 58 (1.72%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
CAMPYLOBACTER INFECTION	Additional description: CAMPYLOBACTER INFECTION		
subjects affected / exposed	2 / 58 (3.45%)	0 / 55 (0.00%)	
occurrences (all)	2	0	
EPSTEIN BARR VIRUS INFECTION	Additional description: EPSTEIN BARR VIRUS INFECTION		
subjects affected / exposed	1 / 58 (1.72%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
HEPATITIS C	Additional description: HEPATITIS C		
subjects affected / exposed	1 / 58 (1.72%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
ORAL CANDIDIASIS	Additional description: ORAL CANDIDIASIS		
subjects affected / exposed	0 / 58 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
SHIGELLA INFECTION	Additional description: SHIGELLA INFECTION		
subjects affected / exposed	0 / 58 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
URINARY TRACT INFECTION	Additional description: URINARY TRACT INFECTION		

subjects affected / exposed	0 / 58 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
HYPERGLYCAEMIA	Additional description: HYPERGLYCAEMIA		
subjects affected / exposed	0 / 58 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
HYPOKALEMIA	Additional description: HYPOKALEMIA		
subjects affected / exposed	1 / 58 (1.72%)	1 / 55 (1.82%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 May 2018	Amendment 3 - Updated protocol to v2.0 to reflect the addition of more sites in the initial phase of the trial
18 January 2019	Amendment 4 - Addition of new sites
12 March 2019	Amendment 5 - Addition of new sites
04 April 2019	Amendment 6 - Addition of new sites
22 May 2019	Amendment 7 - Addition of new site
10 June 2019	Amendment 8 - Addition of new site
01 July 2019	Amendment 9 - Addition of new site
24 September 2019	Amendment 10 - Addition of new site
13 January 2021	Amendment 12 - Change of PI at Cardiff site

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
23 March 2020	Trial recruitment was delayed due to the COVID-19 lockdown, usually due to the reallocation of staff resources. The trial was not formally paused or restarted but this did have an impact.	-

Notes:

Limitations and caveats

None reported