



Clinical trial results:

Phase II trial of interleukin-1 receptor antagonist in intracerebral haemorrhage: BLOcking the Cytokine IL-1 in ICH

Summary

EudraCT number	2018-000249-38
Trial protocol	GB
Global end of trial date	30 April 2021

Results information

Result version number	v1 (current)
This version publication date	05 March 2023
First version publication date	05 March 2023

Trial information

Trial identification

Sponsor protocol code	R118439
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03737344
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	The University of Manchester
Sponsor organisation address	Oxford Road, Manchester, United Kingdom, M13 9PT
Public contact	Mohammed Zubair, University of Manchester , clinicaltrials@manchester.ac.uk
Scientific contact	Mohammed Zubair, University of Manchester , clinicaltrials@manchester.ac.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	26 January 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 February 2021
Global end of trial reached?	Yes
Global end of trial date	30 April 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine whether interleukin-1 receptor antagonist (IL-1Ra (Anakinra / Kineret®)) reduce subacute perihæmatomal oedema after intracerebral haemorrhage (ICH).

Protection of trial subjects:

Side effects vary from patient to patient and all patients will be monitored closely and given appropriate medication to reduce side effects. Patients are informed of common side effects, risks and potential benefits of the trial in the Participant Information Sheet. Patients are asked to inform their medical team of any changes in their health, whether or not they think it is related to the medication. Investigators may ask patients to stop treatment or might reduce the dose of the drugs should they have any unexpected side effects or other illnesses which occur as a result of treatment.

Any SAEs and SUSARs will be reported in line with GCP and Trust reporting requirements. Changes in the emerging safety profile of Anakinra (as detailed in the Investigator's brochure) or any finding in this clinical trial will be monitored and patients will receive amended Participant Information Sheets and be asked to reconsent to the trial as and when required.

Background therapy:

The care for all patients in the trial will be identical to the standard care pathway which will continue as normal including acute management of anticoagulant reversal, blood pressure lowering, intensive or high dependency care, rehabilitation, and clinical follow-up. No treatment will be withheld as a result of participating in the trial and participation will not affect clinical care.

Evidence for comparator:

The prototypical, proinflammatory cytokine IL-1 plays a key role in the early damaging inflammatory response in the brain and inhibiting IL-1 leads to a reduction in damage in diverse experimental acute brain injuries including ischaemic stroke, excitotoxicity, traumatic brain injury, and ICH. We have recently shown that IL-1 alpha (IL-1 α), IL-1 beta (IL-1 β) and IL-1Ra are all present in high concentrations in serial haematoma fluid collected from acute ICH patients taking part in the MISTIE III trial. IL-1 is also rapidly upregulated in perihæmatomal brain tissue from animal models of ICH and from ICH patients. The naturally occurring IL-1 blocker, IL-1Ra (Kineret®), is expressed at almost undetectable levels in healthy brain.

A randomised, controlled, phase 2 trial of an intravenous (IV) infusion of IL-1Ra in acute stroke undertaken at Salford Royal NHS Foundation Trust (SRFT), demonstrated a significant reduction in inflammatory markers as well as reversal of stroke-related peripheral immunosuppression. More recently, it has become apparent that IL-1 has detrimental actions in both the brain and systemically in animal models of cerebral ischaemia, suggesting that IL-1 blocking treatments may not need to cross the blood-brain barrier to confer benefit in ischaemic stroke and prompting the use of much lower subcutaneous (SC) doses of IL-1Ra. A further randomised controlled phase 2 trial of SC IL-1Ra (100 mg BD for 3 days) tested this approach in 80 ischaemic stroke patients at SRFT has also demonstrated a significant reduction in plasma IL-6 and CRP.

A single-centre, randomised, controlled phase 2 trial of SC IL-1Ra (100 mg OD for 5 days) in 20 patients with severe traumatic brain injury has shown IL-1Ra to be safe in this pathology, and penetrated in to plasma and brain extracellular fluid. A reduction in macrophage-derived chemoattractant within the brain of IL-1Ra treated patients was detected by microdialysis.

Actual start date of recruitment	15 March 2019
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: 25
Worldwide total number of subjects	25
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)	0
Adults (18-64 years)	10
From 65 to 84 years	12
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Patients with acute intra-cerebral haemorrhage were recruited for the trial. Patients with ICH recruited from Hyper Acute Stroke Units (HASUs) in the UK. Adults admitted to a participating centre with a clinical diagnosis of acute ICH also considered for trial participation.

Pre-assignment

Screening details:

Patients with spontaneous, non-traumatic, supratentorial ICH with no underlying macrovascular or neoplastic cause admitted to a participating centre within 8 hours of symptom onset.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subcutaneous injection of matched placebo

Arm type	Placebo
Investigational medicinal product name	Placebo (Manufactured by Sobi AB)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Solution for injection , Subcutaneous use

Dosage and administration details:

Subcutaneous injection of 100mg matched placebo (manufactured by Sobi AB) prepared in 0.67mL prefilled syringe for single use. Administered as soon as possible after randomisation. Continued twice daily (with a minimum of 8h and a maximum of 16h between doses) for up to 3 days (6 doses) from onset of symptoms or until discharge from the treating centre (whichever sooner).

Arm title	Anakinra
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Arm description:

Subcutaneous injection of Anakinra

Arm type	Experimental
Investigational medicinal product name	Anakinra
Investigational medicinal product code	
Other name	Kineret®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injection of 100mg Interleukin-1 receptor antagonist (IL-1Ra) Kineret® (Anakinra) prepared in 0.67mL prefilled syringe for single use. Administered as soon as possible after randomisation. Continued twice daily (with a minimum of 8h and a maximum of 16h between doses) for up to 3 days (6 doses) from onset of symptoms or until discharge from the treating centre (whichever sooner).

Number of subjects in period 1	Placebo	Anakinra
Started	11	14
Completed	11	14

Period 2

Period 2 title	72 Hours
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subcutaneous injection of matched placebo

Arm type	Placebo
Investigational medicinal product name	Placebo (Manufactured by Sobi AB)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Solution for injection , Subcutaneous use

Dosage and administration details:

Subcutaneous injection of 100mg matched placebo (manufactured by Sobi AB) prepared in 0.67mL prefilled syringe for single use. Administered as soon as possible after randomisation. Continued twice daily (with a minimum of 8h and a maximum of 16h between doses) for up to 3 days (6 doses) from onset of symptoms or until discharge from the treating centre (whichever sooner).

Arm title	Anakinra
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Arm description:

Subcutaneous injection of Anakinra

Arm type	Experimental
Investigational medicinal product name	Anakinra
Investigational medicinal product code	
Other name	Kineret®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injection of 100mg Interleukin-1 receptor antagonist (IL-1Ra) Kineret® (Anakinra) prepared in 0.67mL prefilled syringe for single use. Administered as soon as possible after randomisation. Continued twice daily (with a minimum of 8h and a maximum of 16h between doses) for up to 3 days (6 doses) from onset of symptoms or until discharge from the treating centre (whichever sooner).

Number of subjects in period 2	Placebo	Anakinra
Started	11	14
Completed	11	12
Not completed	0	2
Adverse event, serious fatal	-	1
Consent withdrawn by subject	-	1

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Subcutaneous injection of matched placebo	
Reporting group title	Anakinra
Reporting group description:	
Subcutaneous injection of Anakinra	

Reporting group values	Placebo	Anakinra	Total
Number of subjects	11	14	25
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)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	4	6	10
From 65-84 years	6	6	12
85 years and over	1	2	3
Gender categorical			
Units: Subjects			
Female	6	6	12
Male	5	8	13
Ethnicity			
Units: Subjects			
White	9	12	21
Mixed	0	0	0
Asian / Asian British	1	0	1
Black / Black British	1	2	3
Chinese	0	0	0
Other	0	0	0
Premorbid mRS (modified Rankin Scale)			
Units: Subjects			
0 No Residual Symptoms	7	12	19
1 No significant disability	3	0	3
2 Slight disability	0	0	0
3 Moderate disability	1	2	3
4 Moderately severe disability	0	0	0
5 Severe disability	0	0	0
6 Unable to determine	0	0	0
Glasgow Coma Score Classification			
Units: Subjects			
Mild (14-15)	1	1	2

Moderate (9-13)	1	4	5
Severe (3-8)	9	9	18
NIHSS on admission/baseline			
Units: Subjects			
Minor (1-4)	5	1	6
Moderate (5-15)	4	8	12
Moderate-severe (16-20)	2	3	5
Severe (21-40)	0	2	2
Intraventricular haemorrhage			
Units: Subjects			
Yes	1	4	5
No	10	10	20
Haematoma location			
Units: Subjects			
Deep	8	7	15
Lobar	3	7	10
Hypertension			
Units: Subjects			
Yes	5	7	12
No	5	7	12
Unknown	1	0	1
Type 1 Diabetes			
Units: Subjects			
Yes	0	0	0
No	11	14	25
Type 2 Diabetes			
Units: Subjects			
Yes	1	0	1
No	10	14	24
Atrial fibrillation			
Units: Subjects			
Yes	3	3	6
No	1	0	1
Missing	7	11	18
Mechanical heart valve			
Units: Subjects			
Yes	0	0	0
No	4	3	7
Unknown	7	11	18
Venous thromboembolism			
Units: Subjects			
Yes	1	0	1
No	3	3	6
Missing	7	11	18
Use of antithrombotic drugs			
Units: Subjects			
Aspirin	0	0	0
Dipyridamole (Asasantin, Persantin)	0	0	0
Clopidogrel	0	0	0
Warfarin	0	3	3
Sinthrome	0	0	0

Rivaroxaban	2	0	2
Apixaban	2	0	2
Edoxaban	0	0	0
Dabigaltran	0	0	0
Other	0	0	0
None of the above	7	11	18
Time between onset and arrival in hospital			
Units: Hours			
median	1.8	1.6	
full range (min-max)	1.1 to 4.8	0.9 to 5.6	-
Systolic Blood Pressure			
Units: millimetres of mercury (mmHg)			
arithmetic mean	158.7	160.7	
standard deviation	± 22.3	± 30.7	-
ICH volume			
Units: ml			
median	5.5	12.6	
inter-quartile range (Q1-Q3)	2.1 to 10.9	1.4 to 41.8	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Subcutaneous injection of matched placebo	
Reporting group title	Anakinra
Reporting group description: Subcutaneous injection of Anakinra	
Reporting group title	Placebo
Reporting group description: Subcutaneous injection of matched placebo	
Reporting group title	Anakinra
Reporting group description: Subcutaneous injection of Anakinra	

Primary: Oedema extension distance (OED) at 72 hours

End point title	Oedema extension distance (OED) at 72 hours
End point description: Oedema extension distance (OED) at 72 hours. Calculated as a derivative from The volume of perihaematomal oedema (PHO vol) and of the haematoma (ICH vol)	
End point type	Primary
End point timeframe: Oedema extension distance (OED) at 72 hours from Baseline	

End point values	Placebo	Anakinra	Placebo	Anakinra
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	14	11	13
Units: derived value (decimal)				
arithmetic mean (standard deviation)				
Mean (descriptive)	0.7 (± 0.6)	1.0 (± 0.9)	1.4 (± 1.2)	1.7 (± 1.3)
Mean change (72hr - baseline) (Descriptive)	0.6 (± 0.7)	0.6 (± 0.7)	0.6 (± 0.7)	0.6 (± 0.7)

Statistical analyses

Statistical analysis title	ANCOVA of OED
Statistical analysis description: The primary analysis was an analysis of covariance (ANCOVA) which adjusted for baseline value of OED. Analyses conducted using 95% confidence intervals. No formal adjustments made for multiplicity as there is a single primary analysis. Given small sample size, interpretation largely descriptive with no hypothesis testing.	
Comparison groups	Placebo v Anakinra

Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
Parameter estimate	Mean difference (final values)
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.74
upper limit	0.51

Notes:

[1] - Primary analysis conducted under the principle of intention to treat and analysis of covariance adjusted for baseline value of OED.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

adverse event monitoring performed during the study treatment period. Further clinical assessments for safety monitoring at baseline, before the 2nd Investigational Medicinal Product (IMP) administration, on Day 4 and on Day 30 post randomisation.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	Uncoded
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Dictionary version	NA
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Reporting groups

Reporting group title	Anakinra
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Reporting group description: -	
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Reporting group title	Placebo
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Reporting group description: -	
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Serious adverse events	Anakinra	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 14 (35.71%)	1 / 11 (9.09%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Incidental bladder lesion	Additional description: Incidental bladder lesion		
subjects affected / exposed	1 / 14 (7.14%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac Arrhythmia	Additional description: Cardiac Arrhythmia		
subjects affected / exposed	1 / 14 (7.14%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Inflammatory Amyloid Angiopathy	Additional description: Inflammatory Amyloid Angiopathy		
subjects affected / exposed	0 / 14 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracerebral Hemorrhage	Additional description: Intracerebral Hemorrhage		

subjects affected / exposed	2 / 14 (14.29%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large left basal ganglia bleed	Additional description: Large left basal ganglia bleed		
subjects affected / exposed	1 / 14 (7.14%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Aspiration Pneumonia	Additional description: Aspiration Pneumonia		
subjects affected / exposed	2 / 14 (14.29%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Emboli	Additional description: Pulmonary Emboli		
subjects affected / exposed	1 / 14 (7.14%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypernatremia	Additional description: Hypernatremia		
subjects affected / exposed	1 / 14 (7.14%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Anakinra	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 14 (14.29%)	3 / 11 (27.27%)	
Nervous system disorders			
Sciatica	Additional description: Sciatica		
subjects affected / exposed	0 / 14 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Seizure	Additional description: Seizure		
subjects affected / exposed	1 / 14 (7.14%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
General disorders and administration			

site conditions Pyrexia subjects affected / exposed occurrences (all)	Additional description: Pyrexia		
	1 / 14 (7.14%)	0 / 11 (0.00%)	
	1	0	
Respiratory, thoracic and mediastinal disorders Aspiration Pneumonia subjects affected / exposed occurrences (all)	Additional description: Aspiration Pneumonia		
	0 / 14 (0.00%)	1 / 11 (9.09%)	
	0	1	
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	Additional description: Rash		
	0 / 14 (0.00%)	1 / 11 (9.09%)	
	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 May 2019	SA01 - Removal of Stoke as a study site. Addition of Aberdeen as a study site.
11 September 2019	SA02 - Addition of 'pre notification pack' for 3 month follow up where the patient was consented via representative. Removal of pre IMP requirement for blood samples (excluding 1st sample)
17 March 2020	SA03 - Addition of study sites. Extension to the recruitment period. Change to the IMP administration window and update to exclusion criteria. Formatting change to ICF and typographical correction on GP Letter. Update to SmPC.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported