Clinical trial results:
Does subcutaneous interleukin-1 receptor antagonist reduce inflammation following subarachnoid haemorrhage?

Summary

EudraCT number	2011-001855-35
Trial protocol	GB
Global end of trial date	13 October 2015

Results information

Result version number	v1 (current)
This version publication date	29 November 2019
First version publication date	29 November 2019
Summary attachment (see zip file)	publication SCIL-SAH JNS (SCIL-SAH.pdf)

Trial information

Trial identification

Sponsor protocol code	2011.087neuro

Additional study identifiers

ISRCTN number	ISRCTN25048895
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	SALFORD ROYAL NHS FOUNDATION TRUST
Sponsor organisation address	ECCLES NEW ROAD, SALFORD, United Kingdom, M5 5AP
Public contact	Prof Andrew King (Pippa Tyrrell, original CI has retired), Salford Royal NHS Foundation Trust, 44 1612064265, andrew.king@manchester.ac.uk
Scientific contact	Prof Andrew King (Pippa Tyrrell, original CI has retired), Salford Royal NHS Foundation Trust, 44 1612064265, andrew.king@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	13 October 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 October 2015
Global end of trial reached?	Yes
Global end of trial date	13 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

What effect does the specific anti-inflammatory drug (IL-1Ra) have on the levels of a specific inflammatory protein (IL-6) in blood between 3-8 days after a brain haemorrhage?

Protection of trial subjects:

The known risks associated with sampling of blood and from administering the investigational medicinal product via subcutaneous route were managed by the research team. Blood samples were collected from existing venous/arterial lines whenever possible and research blood sampling was collected at the same time as clinical blood samples to minimise the risk of pain/discomfort for participants. Administration of IMP in the treatment group was subcutaneous and site of administration was varied for each injection to avoid risk of injection site reaction and bruising. IMP was administered slowly and warmed to room temperature prior to administration in line with SPC, to minimise discomfort.

Background therapy:

Open-label, randomised trial of interleukin-1 receptor antagonist (IL-1Ra). No placebo

Evidence for comparator:

No comparator

Actual start date of recruitment	17 October 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 136
Worldwide total number of subjects	136
EEA total number of subjects	136

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)	114
From 65 to 84 years	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants meeting eligibility were recruited from three NHS hospital sites in England between 17/10/2011 and 07/11/2014.
Participants were followed up at 6 months post subarachnoid haemorrhage by telephone and outcome assessed using Glasgow Outcome score (secondary outcome). Final telephone outcome assessment performed May, 2015

Pre-assignment

Screening details:

Patients presenting to neurosurgical centres within 72h of onset of spontaneous subarachnoid haemorrhage (SAH) were screened for eligibility to participate (473). In addition to exclusion criteria reasons for not recruitment were late presentation to site, unable to confirm aneurysm within timeframe, no consent available

Period 1

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

Blinding implementation details:

laboratory staff were blinded to treatment arm

Arms

Are arms mutually exclusive?	Yes
Arm title	treatment arm

Arm description:

Participant randomised to receive twice daily subcutaneous injections of investigational drug (interleukin-1 receptor antagonist; IL-1Ra/anakinra)

Arm type	Experimental
Investigational medicinal product name	interleukin-1 receptor antagonist; IL-1Ra/anakinra
Investigational medicinal product code	L04AA14
Other name	Kineret, L04AC03
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

100mg in 0.6ml pre-filled syringe administered twice daily (12hourly intervals) for maximum of 21 days from symptom-onset (ictus)

Arm title	control arm

Arm description:

Participants randomised to standard care without addition of IMP. Participants completed all other protocol/assessment

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	treatment arm	control arm
Started	68	68
Completed	61	64
Not completed	7	4
Consent withdrawn by subject	7	4

Baseline characteristics

Reporting groups	
Reporting group title	treatment arm
Reporting group description:	
Participant randomised to receive twice daily subcutaneous injections of investigational drug (interleukin-1 receptor antagonist; IL-1Ra/anakinra)	
Reporting group title	control arm
Reporting group description:	
Participants randomised to standard care without addition of IMP. Participants completed all other protocol/assessment	

Reporting group values	treatment arm	control arm	Total
Number of subjects	68	68	136
Age categorical			
participants randomised to trial			
Units: Subjects			
18-80	68	68	136
Gender categorical Units: Subjects			
Female	56	51	107
Male	12	17	29

End points

End points reporting groups

Reporting group title	treatment arm
Reporting group description:	
Participant randomised to receive twice daily subcutaneous injections of investigational drug (interleukin-1 receptor antagonist; IL-1Ra/anakinra)	
Reporting group title	control arm
Reporting group description:	
Participants randomised to standard care without addition of IMP. Participants completed all other protocol/assessment	

Primary: Change in levels of IL-6 between treated and untreated groups

End point title	Change in levels of IL-6 between treated and untreated groups
End point description:	
Linear measurement of plasma IL-6 collected daily from baseline (within 72 hours of onset of subarachnoid haemorrhage) to day 8 post symptom onset between treated and untreated groups	
End point type	Primary
End point timeframe:	
Plasma IL-6 concentrations daily from baseline (pre-randomisation) to day 8 post ictus	

End point values	treatment arm	control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	64		
Units: ng/ml				
log mean (full range (min-max))	4.48 (3.28 to 5.68)	4.48 (3.28 to 5.68)		

Statistical analyses

Statistical analysis title	statistical analysis
Statistical analysis description:	
The primary outcome measure was the area under the curve (AUC) for natural log (ln) (IL-6) from Days 3 to 8. Patients were included in the analysis if they provided ≥ 4 blood samples from a possible total of 6. Secondary outcomes were corresponding AUCs for other biomarkers, all biomarkers up to Day 21, and Glasgow Outcome Scale–extended (GOS-E) score at 6 months. Sample size calculation was based on effects observed for ln(IL-6) and ln(CRP) after 72 hours of IV infusion in patients wit	
Comparison groups	treatment arm v control arm
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.005
Method	Regression, Logistic

Notes:
[1] - Area under curve

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treated group

Adverse event reporting additional description:

Adverse events for participants who received at least one dose of IMP within 72h of SAH to day 21 post SAH

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	treatment arm

Reporting group description:

Participant randomised to receive twice daily subcutaneous injections of investigational drug (interleukin-1 receptor antagonist; IL-1Ra/anakinra)

Reporting group title	control arm

Reporting group description:

Participants randomised to standard care without addition of IMP. Participants completed all other protocol/assessment

Serious adverse events	treatment arm	control arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	49 / 68 (72.06%)	40 / 68 (58.82%)	
number of deaths (all causes)	3	5	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Cardiac dysfunction	Additional description: Cardiac events (all causes)		
subjects affected / exposed	2 / 68 (2.94%)	2 / 68 (2.94%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Neurological symptom	Additional description: Neurological event, including deterioration in neurological function		
subjects affected / exposed	25 / 68 (36.76%)	24 / 68 (35.29%)	
occurrences causally related to treatment / all	0 / 25	0 / 24	
deaths causally related to treatment / all	0 / 2	0 / 3	
Infections and infestations			
Respiratory tract infection	Additional description: Respiratory infection (any cause)		

subjects affected / exposed	8 / 68 (11.76%)	7 / 68 (10.29%)	
occurrences causally related to treatment / all	0 / 8	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 2	
Urinary tract infection	Additional description: urinary tract infection (all causes)		
subjects affected / exposed	4 / 68 (5.88%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Central nervous system infection	Additional description: Infection of central nervous system (all causes)		
subjects affected / exposed	2 / 68 (2.94%)	3 / 68 (4.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia	Additional description: Pyrexia of unknown origin		
subjects affected / exposed	3 / 68 (4.41%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Metabolic disorder	Additional description: Metabolic events (all causes)		
subjects affected / exposed	1 / 68 (1.47%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	

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

Non-serious adverse events	treatment arm	control arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 68 (69.12%)	55 / 68 (80.88%)	
Cardiac disorders			
Cardiac dysfunction	Additional description: non serious cardiac dysfunction		
subjects affected / exposed	3 / 68 (4.41%)	2 / 68 (2.94%)	
occurrences (all)	3	2	
Nervous system disorders			
Neurological symptom	Additional description: Non-serious Neurological events (all causes)		
subjects affected / exposed	12 / 68 (17.65%)	7 / 68 (10.29%)	
occurrences (all)	12	7	
Infections and infestations			

Respiratory tract infection	Additional description: Respiratory tract events (all causes)		
subjects affected / exposed	2 / 68 (2.94%)	4 / 68 (5.88%)	
occurrences (all)	2	4	
Pyrexia	Additional description: non-serious pyrexia of unknown origin		
subjects affected / exposed	9 / 68 (13.24%)	11 / 68 (16.18%)	
occurrences (all)	9	11	
Urinary tract infection	Additional description: non serious UTI		
subjects affected / exposed	4 / 68 (5.88%)	9 / 68 (13.24%)	
occurrences (all)	4	9	
Skin infection	Additional description: non serious skin infection		
subjects affected / exposed	1 / 68 (1.47%)	2 / 68 (2.94%)	
occurrences (all)	1	2	
Metabolism and nutrition disorders			
Metabolic function test abnormal	Additional description: non serious abnormal metabolic function		
subjects affected / exposed	7 / 68 (10.29%)	14 / 68 (20.59%)	
occurrences (all)	7	14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 April 2012	A. To undertake extra analysis on blood collected from trial participants; B. To invite trial participants to participate in a sub-study if they have an external ventricular drain (EVD) inserted as part of their clinical care; C. To recruit a number of healthy volunteers to act as controls to the participants in the main trial.
01 April 2013	Addition of two new research sites Amendment to protocol on conduct of the study at the new sites Amendment to documents in initial application i.e. additional patient information/consent for new study sites, Amendment to protocol regarding extension of timeframe for 6 month outcome assessment Amendment to protocol regarding submission of adverse event reports to study Sponsor Extension to study period of 12 months
12 December 2013	outlining the temporary arrangements to cover absence of the Chief Investigator
24 March 2014	reinstatement of Prof Pippa Tyrrell as Chief Investigator
27 April 2015	Permission to collect additional outcome information on participants recruited to the trial at Salford Royal NHS Foundation Trust

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28298024