



## Clinical trial results:

### Does subcutaneous interleukin-1 receptor antagonist reduce inflammation following ischaemic stroke compared to placebo?

#### Summary

EudraCT number	2013-001757-28
Trial protocol	GB
Global end of trial date	28 February 2017

#### Results information

Result version number	v1 (current)
This version publication date	29 November 2019
First version publication date	29 November 2019

#### Trial information

##### Trial identification

Sponsor protocol code	2013/066st
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##### Additional study identifiers

ISRCTN number	ISRCTN74236229
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Salford Royal NHS Foundation Trust
Sponsor organisation address	Stott Lane, SALFORD, United Kingdom, M6 8HD
Public contact	SMITH, SALFORD ROYAL NHS FOUNDATION TRUST, 44 01612060623, craig.smith-2@manchester.ac.uk
Scientific contact	CRAIG, SALFORD ROYAL NHS FOUNDATION TRUST, +44 01612060623, craig.smith-2@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:

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**Results analysis stage**

Analysis stage	Final
Date of interim/final analysis	16 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 November 2016
Global end of trial reached?	Yes
Global end of trial date	28 February 2017
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

Main objective of the trial:

To determine the effect of a specific type of anti-inflammatory drug (Interleukin-1 receptor antagonist; IL-1Ra), which is administered as an injection into the skin, have on levels of an inflammation-causing protein (Interleukin-6; IL-6) in blood samples taken between 6 hours and 5-7 days after the onset of a stroke.

Protection of trial subjects:

Research blood samples collected at same time as those required for clinical purposes (where possible)

Background therapy:

Participation in the trial did not impact on clinical care and no standard treatments were withheld.

Evidence for comparator:

Interleukin-1 receptor antagonist found to reduce inflammatory markers (IL-6 and CRP) in early phase and experimental models of stroke.

Actual start date of recruitment	02 December 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	United Kingdom: 80
Worldwide total number of subjects	80
EEA total number of subjects	80

Notes:

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**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)	15

From 65 to 84 years	53
85 years and over	12

## Subject disposition

### Recruitment

Recruitment details:

Participants recruited to a single-centre, UK site between 1/3/14 and 31/10/16

### Pre-assignment

Screening details:

Aged over 18

Within 6h of confirmed ischaemic stroke

### Period 1

Period 1 title	0-72 hours (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

Third party web-based randomisation system, stratified for age, severity and thrombolysis

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Treatment arm

Arm description:

Participants who received at least one dose of IMP within 6 hours of stroke onset (maximum 6 doses within 72 hours of stroke)

Arm type	Active comparator
Investigational medicinal product name	Interleukin-1 receptor antagonist
Investigational medicinal product code	EU/1/02/203/001-003
Other name	anakinra, kineret
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

100MG in 0.6ml, twice-daily for 3 days. First dose within 6 hours of onset of stroke symptoms. All doses complete within 72 hours of stroke onset

<b>Arm title</b>	Control arm
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Arm description:

Participants who received at least one dose of placebo within 6 hours of stroke onset (maximum 6 doses within 72 hours of stroke onset)

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	EU/1/02/203/001-003
Other name	placebo
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

twice daily injection 0.6ml maximum 6 doses within 72 hours of stroke onset

<b>Number of subjects in period 1</b>	Treatment arm	Control arm
Started	39	41
primary outcome IL-6/CRP days 1-3	39	41
Completed	39	41

## Baseline characteristics

### Reporting groups

Reporting group title	Treatment arm
Reporting group description: Participants who received at least one dose of IMP within 6 hours of stroke onset (maximum 6 doses within 72 hours of stroke)	
Reporting group title	Control arm
Reporting group description: Participants who received at least one dose of placebo within 6 hours of stroke onset (maximum 6 doses within 72 hours of stroke onset)	

Reporting group values	Treatment arm	Control arm	Total
Number of subjects	39	41	80
Age categorical			
Adults over 18 (all ages)			
Units: Subjects			
All adults over 18	39	41	80
Gender categorical			
Units: Subjects			
Female	17	13	30
Male	22	28	50

## End points

### End points reporting groups

Reporting group title	Treatment arm
Reporting group description: Participants who received at least one dose of IMP within 6 hours of stroke onset (maximum 6 doses within 72 hours of stroke)	
Reporting group title	Control arm
Reporting group description: Participants who received at least one dose of placebo within 6 hours of stroke onset (maximum 6 doses within 72 hours of stroke onset)	

### Primary: AUC IL-6

End point title	AUC IL-6
End point description: The primary analysis used linear regression to control for the randomization stratification criteria and for the baseline value of log(IL-6). Where one of the day 1 to day 3 blood samples was unavailable, imputation was undertaken. The fitted value from linear regression of log(IL-6) on "day" was substituted for the missing value.	
End point type	Primary
End point timeframe: Day 1-3	

End point values	Treatment arm	Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28 <sup>[1]</sup>	35 <sup>[2]</sup>		
Units: log10 enzyme-linked immunosorbent ass...				
number (confidence interval 95%)	1.72 (1.28 to 2.17)	1.72 (1.28 to 21.7)		

Notes:

[1] - 28 participants with sufficient samples to meet primary outcome

[2] - 35 participants with sufficient data to meet primary outcome

### Statistical analyses

Statistical analysis title	statistical analysis
Statistical analysis description: All analyses were prespecified in a statistical analysis plan before study completion and unblinding of the data set. Demographic and clinical data at baseline were tabulated by allocated test treatment. The primary analysis used linear regression to control for the randomization stratification criteria and for the baseline value of log(IL-6).	
Comparison groups	Treatment arm v Control arm

Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	equivalence <sup>[3]</sup>
P-value	< 0.005
Method	regression coefficient
Parameter estimate	Mean difference (final values)

Notes:

[3] - Linear regression to control



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

30 days of first dose of IMP

Adverse event reporting additional description:

If the adverse event is on-going at 30 days, the participant will be followed up until the event has resolved / stabilised / been fully investigated to the satisfaction of the PI and the study Sponsor or the participant is discharged from the study centre

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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### Reporting groups

Reporting group title	Treatment arm
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Reporting group description:

Participants who received at least one dose of IMP within 6 hours of stroke onset (maximum 6 doses within 72 hours of stroke)

Reporting group title	Control arm
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Reporting group description:

Participants who received at least one dose of placebo within 6 hours of stroke onset (maximum 6 doses within 72 hours of stroke onset)

Serious adverse events	Treatment arm	Control arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 39 (12.82%)	9 / 41 (21.95%)	
number of deaths (all causes)	3	5	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Haemorrhagic transformation stroke			
subjects affected / exposed	3 / 39 (7.69%)	2 / 41 (4.88%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Nervous system disorders			
Neurological symptom	Additional description: Includes deterioration in neurological function, persistent or transient and seizure		
subjects affected / exposed	0 / 39 (0.00%)	3 / 41 (7.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory arrest			

subjects affected / exposed	1 / 39 (2.56%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Infections and infestations</b>			
Pneumonia	Additional description: Includes general diagnosis of chest infection, upper and lower respiratory tract infection		
subjects affected / exposed	1 / 39 (2.56%)	6 / 41 (14.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 2	

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

<b>Non-serious adverse events</b>	Treatment arm	Control arm	
<b>Total subjects affected by non-serious adverse events</b>			
subjects affected / exposed	7 / 39 (17.95%)	12 / 41 (29.27%)	
<b>Injury, poisoning and procedural complications</b>			
Haemorrhagic transformation stroke	Additional description: Evidence of haemorrhagic transformation of stroke on 24h brain imaging but asymptomatic		
subjects affected / exposed	3 / 39 (7.69%)	2 / 41 (4.88%)	
occurrences (all)	3	2	
Bleeding time	Additional description: bleeding from ear post thrombolysis		
subjects affected / exposed	0 / 39 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
<b>Cardiac disorders</b>			
Arrhythmia	Additional description: atrial fibrillation		
subjects affected / exposed	0 / 39 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Cardiac dysfunction	Additional description: includes increased cardiac enzyme result, syncopal episode		
subjects affected / exposed	1 / 39 (2.56%)	1 / 41 (2.44%)	
occurrences (all)	1	1	
<b>Nervous system disorders</b>			
Neurological symptom	Additional description: Includes transient deterioration in neurological function and existing diagnosis of seizure		
subjects affected / exposed	0 / 39 (0.00%)	2 / 41 (4.88%)	
occurrences (all)	0	2	
<b>Infections and infestations</b>			
Pneumonia	Additional description: Non serious chest infection classed as pneumonia		

subjects affected / exposed	0 / 39 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Vaginal infection			
subjects affected / exposed	1 / 39 (2.56%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	2 / 39 (5.13%)	2 / 41 (4.88%)	
occurrences (all)	2	2	
Diarrhoea infectious	Additional description: clostridium difficile		
subjects affected / exposed	1 / 39 (2.56%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Bursitis infective			
subjects affected / exposed	0 / 39 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Pyrexia	Additional description: Pyrexia of unknown origin		
subjects affected / exposed	0 / 39 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 December 2013	temporary arrangements to cover absence of the Chief Investigator
24 March 2014	Prof Pippa Tyrrell be reinstated as Chief Investigator
05 April 2016	Amendment to: <ul style="list-style-type: none"><li>• Assessment/blood sampling schedule to remove the 5-7 day assessment/sample</li><li>• Inclusion/exclusion criteria</li><li>• Inclusion of immune suppression analysis (changes to participant information and inclusion of matched controls)</li><li>• Change to Sponsor details and other members of the research team</li><li>• Minor corrections and clarifications to the protocol</li></ul>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/29567761>