

# Can IL-1ra reduce inflammation and improve clinical outcome following aneurysmal SAH?

<b>Submission date</b> 04/12/2017	<b>Recruitment status</b> No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
<b>Registration date</b> 14/12/2017	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
<b>Last Edited</b> 29/11/2023	<b>Condition category</b> Nervous System Diseases	<input type="checkbox"/> Individual participant data <input type="checkbox"/> Record updated in last year

## Plain English summary of protocol

### Background and study aims

Subarachnoid haemorrhage (SAH) is a bleed onto the surface of the brain. It is usually caused when a weakness (aneurysm) in the wall of a blood vessel within the brain suddenly bursts. It affects up to 6,000 people every year in the UK. Up to half of all patients do not survive long enough to receive hospital treatment and those who do survive, often suffer long-term issues that impact on their daily life. In the hours and days after SAH, patients are at risk of further brain damage due to inflammation (swelling). A protein called interleukin-1 (IL-1) is the main culprit and this triggers a number of other chemicals in the circulation which may lead to physical symptoms similar to stroke but can also cause problems with language, mood, anxiety and fatigue all of which impact most on recovery and returning to work. The effect of IL-1 can be blocked, reduced or even reversed by another protein present naturally in our body; interleukin-1 receptor antagonist (IL-1Ra). A company has produced a man-made version of IL-1Ra, which has been used for many years as an anti-inflammatory treatment for rheumatoid arthritis. Inflammation occurs very early after the initial haemorrhage and can continue for up to 21 days, which means IL-1Ra should be given early and through the risk period to prevent or reduce these symptoms. Our group has successfully tested IL-1Ra in patients with subarachnoid haemorrhage and found it reduces inflammation in the circulation and brain and we now want to establish whether IL-1Ra improves recovery after subarachnoid haemorrhage. The aim of this study is to treat patients with SAD using IL-1Ra subcutaneously twice daily to see if this can improve clinical outcomes.

### Who can participate?

Adults aged 18 and older who have SAH.

### What does the study involve?

Participants are randomly allocated to one of two groups. Those in the first group receive subcutaneous injections of IL-1Ra twice daily for up to 21 days from the onset of their symptoms. Those in the second group receive a placebo (a dummy) twice daily for 21 days. All participants continue to receive the standard care for subarachnoid haemorrhage and participation in this study will not affect or delay this care. Participants provide blood samples

before the treatment, and after 3-5 days to measure levels of inflammatory markers in the blood. Participants are followed up for safety for 30 days and are followed up for six months to assess the impact of the treatment.

What are the possible benefits and risks of participating?

As this is a phase III study it will be made clear to participants that there is no evidence of benefit at this stage. Participants will also be advised that as this study is double-blind and randomised and it will not be known if they will receive study drug or placebo. Evidence from earlier phase studies showed that the study drug reduces inflammation associated with SAH and is safe to use. The results of this study will provide evidence whether reducing inflammation improves outcome and participants may be helping to provide the evidence that may change treatment for SAH in the future.

Where is the study run from?

This study is being run by the University of Manchester (UK) and takes place in hospitals in the UK.

When is the study starting and how long is it expected to run for?

July 2015 to April 2024

Who is funding the study?

National Institute for Health Research (UK)

Who is the main contact?

Jane Pearson, SCIL@manchester.ac.uk

### **Study website**

<https://sites.manchester.ac.uk/scil/>

## **Contact information**

### **Type(s)**

Scientific

### **Contact name**

Ms Jane Pearson

### **Contact details**

Clinical Trial Manager  
Manchester Clinical Trials Unit  
The University of Manchester  
Jean McFarlane Building  
Oxford Road  
Manchester  
United Kingdom  
M13 9PL  
+44 (0)161 918 2142  
SCIL@manchester.ac.uk

## **Additional identifiers**

**EudraCT/CTIS number**

2016-003725-42

**IRAS number**

214739

**ClinicalTrials.gov number**

NCT03249207

**Secondary identifying numbers**

CPMS 35757, IRAS 214739

## **Study information**

**Scientific Title**

Does Interleukin-1 Receptor Antagonist Improve Outcome following aneurysmal Subarachnoid Haemorrhage (aSAH)? A Phase III trial

**Acronym**

SC IL-1Ra in SAH - phase III trial

**Study objectives**

Treatment with IL-1Ra subcutaneously (SC) twice daily to patients with aneurysmal subarachnoid haemorrhage will improve clinical outcome at 6 months.

**Ethics approval required**

Ethics approval required

**Ethics approval(s)**

Approved 03/11/2017, North West - Haydock Research Ethics Committee (3rd Floor - Barlow House, 4 Minshull Street, Manchester, M1 3DZ, United Kingdom; +44 (0)20 7104 8137; haydock.rec@hra.nhs.uk), ref: 17/NW/0581

**Study design**

Randomised; Interventional; Design type: Treatment, Drug

**Primary study design**

Interventional

**Secondary study design**

Randomised controlled trial

**Study setting(s)**

Hospital

**Study type(s)**

Treatment

**Participant information sheet**

Not available in web format, please use the contact details below to request a patient information sheet

## **Health condition(s) or problem(s) studied**

Stroke

## **Interventions**

This is a double-blind, placebo-controlled trial. Patients with aneurysmal subarachnoid haemorrhage receive subcutaneous injections of IL-1Ra or placebo twice daily for up to 21 days from the onset of their symptoms. Blood samples are taken before the start of the intervention and after 3-5 days to measure levels of inflammatory markers in the blood. Participants are followed up for safety until day 30 after the start of the intervention and are followed up after six months to assess the impact of the intervention on clinical outcome.

## **Intervention Type**

Other

## **Phase**

Phase III

## **Primary outcome measure**

Clinical outcome is measured using the modified Rankin Scale (mRS) questionnaire at 6 months.

## **Secondary outcome measures**

1. Mood is measured using the Hospital Anxiety and Depression Scale questionnaire at 6 months
2. Fatigue is measured using the GM-SAT Fatigue question and Fatigue Severity Score questionnaire at 6 months
3. Quality of life is measured using the EQ-5D-5L questionnaire at 6 months

## **Overall study start date**

15/07/2015

## **Completion date**

30/04/2024

# **Eligibility**

## **Key inclusion criteria**

1. Patients with CT positive spontaneous SAH admitted to a participating neurosurgical centre where written informed consent can be obtained and study drug can be administered within 72 hours of ictus
2. No concomitant health problems that, in the opinion of the PI or designee, would interfere with participation, administration of study drug or assessment of outcomes including safety
3. Willing and able to give informed consent or consent available from a patient representative for trial inclusion including agreement in principle to receive study drug and undergo all study assessments
4. Male or female aged 18 years or above

## **Participant type(s)**

Patient

**Age group**

Adult

**Lower age limit**

18 Years

**Sex**

Both

**Target number of participants**

Planned Sample Size: 1000; UK Sample Size: 1000

**Total final enrolment**

612

**Key exclusion criteria**

Current participant exclusion criteria as of 14/08/2023:

1. Unconfirmed or uncertain diagnosis of spontaneous SAH
2. Known active tuberculosis or active hepatitis
3. Known active malignancy
4. Known Still's Disease
5. Neutropenia ( $ANC < 1.5 \times 10^9/L$ )
6. Abnormal renal function (creatinine clearance or estimated Glomerular Filtration Rate (eGFR)  $< 30$  ml/minute) documented in the last 3 months prior to this SAH
7. Live vaccinations within the last 10 days of this SAH
8. Previous or concurrent treatment with IL-1Ra known at the time of trial entry or previous participation in this trial
9. Current treatment with TNF antagonists
10. Known to have participated in a clinical trial of an investigational agent or device in the 30 days prior to ictus
11. Known to have participated in a clinical trial of an investigational agent or device within 5 half-lives (of the previous agent or device) prior to ictus
12. Known to be pregnant or breastfeeding or inability to reliably confirm that the patient is not pregnant
13. Clinically significant serious concurrent medical condition, pre-morbid illnesses, or concurrent serious infection (including confirmed or suspected COVID-19 infection), at the PI's (or designee's) discretion, which could affect the safety or tolerability of the intervention
14. Known allergy to IL-1Ra or any of the excipients listed in the drug SmPC
15. Known allergy to other products that are produced by DNA technology using the microorganism *E. coli* (e.g. *E. coli* derived protein)
16. Current treatment with IL-6 or IL-1 inhibitors or drugs affecting the IL-1 axis
17. History of DRESS syndrome

Previous participant exclusion criteria:

1. Unconfirmed or uncertain diagnosis of spontaneous SAH
2. Known active tuberculosis or active hepatitis
3. Known active malignancy
4. Neutropenia ( $ANC < 1.5 \times 10^9/L$ )
5. Abnormal renal function (creatinine clearance or estimated Glomerular Filtration Rate (eGFR)  $< 30$  ml/minute) documented in the last 3 months prior to this SAH
6. Live vaccinations within the last 10 days of this SAH

7. Previous or concurrent treatment with IL-1Ra known at the time of trial entry or previous participation in this trial
8. Previous or current treatment with medication suspected of interacting with IL-1Ra, listed in the drug SmPC
9. Known to have participated in a clinical trial of an investigational agent or device in the previous 30 days or 5 half-lives of enrolment (whichever is longer) of ictus, or for the period determined by the protocol of the trial / study the patient has taken part in
10. Known to be pregnant or breast feeding or inability to reliably confirm that the patient is not pregnant
11. Clinically significant serious concurrent medical condition, pre morbid illnesses, or concurrent serious infection, at the PI's (or designee's) discretion, which could affect the safety or tolerability of the intervention
12. Known allergy to IL-1Ra or any of the excipients listed in the drug SmPC
13. Known allergy to other products that are produced by DNA technology using the micro-organism E. coli (e.g. E.coli derived protein)

**Date of first enrolment**

31/05/2018

**Date of final enrolment**

30/09/2023

## **Locations**

**Countries of recruitment**

England

Scotland

United Kingdom

Wales

**Study participating centre**

**Royal Stoke University Hospital**

Newcastle Road

Stoke-on-Trent

United Kingdom

ST4 6QG

**Study participating centre**

**Royal Hallamshire Hospital**

Glossop Road

Sheffield

United Kingdom

S10 2JF

**Study participating centre**  
**University Hospital of Wales**  
Heath Park  
Cardiff  
United Kingdom  
CF14 4XW

**Study participating centre**  
**Northern Care Alliance NHS Foundation Trust**  
Salford Royal  
Stott Lane  
Salford  
United Kingdom  
M6 8HD

**Study participating centre**  
**National Hospital for Neurology & Neurosurgery**  
Queen Square  
London  
United Kingdom  
WC1N 3BG

**Study participating centre**  
**Plymouth Hospital**  
Derriford Hospital  
Derriford Road  
Plymouth  
United Kingdom  
PL6 8DH

**Study participating centre**  
**University Hospital Southampton NHS Foundation Trust**  
Southampton General Hospital  
Tremona Road  
Southampton  
United Kingdom  
SO16 6YD

**Study participating centre**

**Leeds General Infirmary**

Great George Street  
Leeds  
United Kingdom  
LS1 3EX

**Study participating centre**

**St George's Hospital**

Blackshaw Road  
London  
United Kingdom  
SW17 0QT

**Study participating centre**

**The Walton Centre NHS Foundation Trust**

Lower Lane  
Fazakerley  
Liverpool  
United Kingdom  
L9 7LJ

**Study participating centre**

**Brighton and Sussex University Hospitals NHS Trust**

Royal Sussex County Hospital  
Eastern Road  
Brighton  
United Kingdom  
BN2 5BE

**Study participating centre**

**Nottingham University Hospitals NHS Trust**

Trust Headquarters  
Queens Medical Centre  
Derby Road  
Nottingham  
United Kingdom  
NG7 2UH

**Study participating centre**

**Charing Cross Hospital**

Fulham Palace Road



London  
United Kingdom  
W6 8RF

**Study participating centre**  
**Barts Health NHS Trust**  
The Royal London Hospital  
80 Newark Street  
London  
United Kingdom  
E1 2ES

**Study participating centre**  
**Southmead Hospital**  
Southmead Road  
Westbury-on-trym  
Bristol  
United Kingdom  
BS10 5NB

**Study participating centre**  
**Lancashire Teaching Hospitals NHS Foundation Trust**  
Royal Preston Hospital  
Sharoe Green Lane  
Fulwood  
Preston  
United Kingdom  
PR2 9HT

**Study participating centre**  
**Addenbrookes**  
Addenbrookes Hospital  
Hills Road  
Cambridge  
United Kingdom  
CB2 0QQ

## **Sponsor information**

**Organisation**

The University of Manchester

**Sponsor details**

Oxford Road  
Manchester  
England  
United Kingdom  
M13 9PL

**Sponsor type**

University/education

**ROR**

<https://ror.org/027m9bs27>

**Funder(s)****Funder type**

Government

**Funder Name**

National Institute for Health Research

**Alternative Name(s)**

National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

**Funding Body Type**

Government organisation

**Funding Body Subtype**

National government

**Location**

United Kingdom

**Results and Publications****Publication and dissemination plan**

Current publication and dissemination plan as of 14/08/2023:

Publication in a high-impact peer reviewed journal is planned and is likely to be in the second half of 2024.

Previous publication and dissemination plan:  
Publication in a high-impact peer reviewed journal is planned and is likely to be in the second half of 2023.

The study protocol is available at <https://www.journalslibrary.nihr.ac.uk/programmes/eme/1420907/#/> (added 04/06/2021)

**Intention to publish date**

30/08/2025

**Individual participant data (IPD) sharing plan**

The data sharing plans for the current study are unknown and will be made available at a later date.

**IPD sharing plan summary**

Data sharing statement to be made available at a later date

**Study outputs**

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">HRA research summary</a>			28/06/2023	No	No
<a href="#">Protocol file</a>	version 8.0	04/06/2020	14/08/2023	No	No
<a href="#">Protocol file</a>	version 9.0	13/03/2023	13/10/2023	No	No