SCIL: Does Interleukin 1 Receptor Antagonist Improve Outcome following Aneurysmal Subarachnoid Haemorrhage (aSAH)? A phase III trial.

Synopsis for Protocol V9 (13Mar2023) dated 10 Aug 2023

Study summary

Subarachnoid haemorrhage (SAH) is most commonly caused when an abnormal bulge in the wall of a blood vessel on the surface of the brain ruptures. 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; many suffer long-term issues that impact on their daily life and return to work e.g. fatigue, attention and memory problems. aSAH in 2005 was estimated to cost £205m annually with community health and social service care estimated to be around 18% of the total. Any treatment that improves clinical outcome would be cost effective.

Previous studies have shown that inflammation in the brain and blood vessels is high after aneurysmal SAH (aSAH) and that it is possible to reduce, block and even reverse this inflammation by administering a man-made version of the protein interleukin-1 receptor antagonist (IL-1Ra) via subcutaneous injection. A phase II trial conducted by Professor Tyrell and her team demonstrated that Kineret® (an IL-1Ra authorised in adults for the treatment of the signs and symptoms of Rheumatoid arthritis) reduced concentration of IL-6 and C-reactive protein in the blood compared to placebo, when administered twice daily for 21 days starting within 3 days of ictus. Furthermore, the phase II trial showed subcutaneous IL-1Ra administration was safe and well tolerated.

This phase III trial now aims to evaluate whether twice daily subcutaneous injection of IL-1Ra (Kineret®) commenced within 72 hours of ictus and administered for up to 21 days post ictus improves the clinical outcome of aSAH patients as assessed by the modified Rankin Scale (mRS) at 6 months.

The phase III trial aims to recruit 800 patients within 72 hours of aSAH from 20 neurosurgical centres in the United Kingdom. Following consent and confirmation of eligibility, participants will be randomly allocated to receive twice-daily subcutaneous injections of IL-1Ra or placebo for a maximum of 21 days after aSAH or until discharge from neurosurgical care. The patient will only be eligible if the first administration of study drug can take place within 72 hours of ictus. Clinical data will be collected at baseline, 3-5 days and 10-12 days post randomisation, and on the final day of study treatment. Blood samples taken prior to randomisation and between 3-5 days after randomisation will be used to assess levels of inflammation through measurement of IL-6 concentration. Safety will be assessed before every drug administration and followed up 30 days after aSAH. Clinical outcome will be assessed 6 months after aSAH by the research team at the University of Manchester and will include assessment of levels of disability, mood, fatigue and quality of life using standard questionnaires conducted over the telephone.

Participant Eligibility Criteria

1.1 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.

1.2 Exclusion criteria

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 breast feeding 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, 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 micro-organism E. coli (i.e. *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.

Schedule of Assessments

Reason	Action	Time point of assessment									
		Screening	**Pre-randomisation**	**Randomisation (Day 0)**	**Prior to each administration of study drug**	**From randomisation until final day of study treatment**	**Day 3-5 post randomisation**	**Day 10-12 post randomisation**	**Final day of study treatment (≤21 days post ictus)**	**Day 30 post randomisation (+/- 3days)**	**Month 6 (post randomisation [b](+/- 28 days)**
Eligibility	Eligibility screen	X									
	Pregnancy test	X									
	Consent		X								
Baseline data	Demographics		X								
	Past clinical history		X								
Mechanism	Research blood (IL-6)		X				X				
	Randomisation			X							
Treatment	Twice daily administration of study drug					X					
Treatment fidelity	Research blood (IL-1Ra)						X				
Safety	Review of clinical blood results by research staff	X					X	X	X	X	
	Ongoing review of clinical condition by clinical staff				X	X					
	Research staff review of clinical data for adverse events and prohibited concomitant medications						X	X	X	X	
	Telephone AE check									X	
Data for collection	Survival check						X		X	X	
	Target aneurysm details						X		X		

	Confirm willingness for 30 day and 6 month follow up								X		
Efficacy	Outcome Assessments: HADS										X
	Outcome Assessments: Fatigue (GM-SAT fatigue										X
	Outcome Assessments: EQ-5D-5L										X
	Outcome assessment: mRS										X
	Outcome assessment: Survival check										X

IMP pathway

Following consent, the participant will be randomised using a bespoke online system, designed for this study and managed by an independent 3rd party. All research staff will be able to log in to this system using their own unique ID. The randomisation system will stratify for grade of SAH, recruitment site and aneurysmal status (confirmed vs unknown). Randomisation will be double-blinded.

The randomisation system will also allow management of kits at site. Part of this management includes maintaining a small supply of study drug kit in a pharmacy standard fridge that can be accessed out of pharmacy working hours (i.e. the fridge is not located in pharmacy). This is to enable recruitment seven days a week. Shipment of kits to site and movement of kits between pharmacy and out-of-pharmacy fridges will also be managed by the randomisation system.

Following randomisation, the system will identify a study drug kit in the out-of-pharmacy fridge. Each kit will contain 7 syringes. Study drug will be administered to participants twice daily, a minimum of 8 hours and a maximum of 16 hours apart. Staff will be required to complete documentation to enable full reconciliation of IMP after each administration and to request resupply of study drug kits from pharmacy to the out-of-pharmacy fridge when an out-of-pharmacy kit is allocated to a participant or when supply in the current kit is running low.

Research costs

Each site will receive a set-up fee to cover research costs of pharmacy set up, IMP management reconciliation and destruction, out of pharmacy fridge calibration and maintenance, staff time in training, monitoring and close out, local trial management and archiving. There will be a per participant fee paid to sites for each participant recruited which will cover staff time in randomisation, blood sampling, data collection, placebo dispensing, and administration and research specific activities associated with Kineret® dispensing and administration. There will be excess treatment costs (ETCs) however these will be covered externally to your trust.