Final End of Study and Safety Report

"The effect of Kineret® on brain biomarkers in patients with subarachnoid haemorrhage"

EudraCT number 2007−005836−98 **Main REC Ref No** 09/MRE09/1

Final Report

Study title: **The effect of Kineret® on brain biomarkers in patients with subarachnoid haemorrhage**.

Funder: Medical Research Council

Chief Investigator: Dr Pippa Tyrrell

Local Investigators: Mr Andrew King (Salford) & Mr Peter Hutchinson (Addenbrooke's)

Study Sponsor: Salford Royal Foundation Hospital (SRFT)

Lead REC: Wales Ethics Committee

Date of Approvals from competent authorities: REC: 29/1/09; MHRA: 11/2/09
SSI: Salford and Trafford LREC and Cambridgeshire 2 LREC. Approval has also been obtained from the University of Manchester Senate Ethics Committee (2/5/09)

Drug: Kineret® (recombinant methyionyl human interleukin-1 receptor antagonist, r-metHuIL-1RA, anakinra) supplied free of charge from Amgen

Study design: Double-blind, randomised placebo controlled trial

Safety reported to: Study Sponsor (SRFT)

Data and Safety review by: Independent Data and Safety Monitoring Committee (IDSMC) after first 10 patients and after last recruited patient follow-up.

Recruitment plan: Patients suffering an aneurysmal subarachnoid haemorrhage (SAH) and requiring external ventricular drain (EVD) insertion for clinical reasons, who satisfied the inclusion and exclusion criteria, were considered for recruitment into the study. The plan was to administer the investigational medicinal product (IMP) in up to 32 participants (16 in each treatment group) across two UK neurosurgical units

Sites: Greater Manchester Neurosciences Centre, based at Salford Royal Foundation Trust (Coordinating site) & Cambridge University Hospitals NHS Foundation Trust (Addenbrooke's Hospital, collaborating site)

Recruitment commenced: 01-06-2009

Purpose of Study: To determine whether intravenously (IV) administered Kineret ® inhibits the central nervous system (CNS) inflammatory response in patients with SAH and to explore the relationship between inflammatory biomarkers in plasma and CSF.

15/02/2011

Results

Patients screened: **254** (Salford: 222; Addenbrookes: 32)
Participants recruited: **18** (Salford 14; Addenbrookes: 4)
Participants withdrawn: **5** (Salford 3; Addenbrookes 2) – No withdrawal were thought to be related to the intervention. One changed their mind prior to IMP administration (Addenbrooke's), one was found to be ineligible prior to IMP (Addenbrooke's), two deteriorated clinically after consent, but prior to IMP administration such that they were unlikely to survive 24 h (both Salford) and, in one patient, the coiling procedure was longer than expected such that the IMP could not be given within 72 h from ictus (Salford).

Participants receiving IMP: **13**

One participant did not complete the 24h infusion. The remaining 12 did.

Serious Adverse Events: **15** – All resolved
No SUSAR/SAR reported

Letter from IDSMC (6/5/10) with details of final review of data and safety enclosed

ID	Site	Age	Sex	Total IMP Dose in mg	Date of IMP	AE number	Date of onset	Description of adverse event
1	Salford	59	M	n/a	n/a	SAE1	5/6/09	Blocked EVD – became ineligible for participation
3	Salford	40	M	17300	10/6/09	SAE1	10/6/09	Raised ICP
4	Salford	49	F	17540	17/6/09	SAE1	18/6/09	Fluctuating GCS
6	Salford	53	F	17300	28/6/09	SAE1	29/6/09	Desaturation
						SAE2	29/6/09	Cardiac arrhythmia
						SAE3	30/6/09	Meningitis
8	Addenbrooke's	69	F	15700	11/7/09	SAE1	10/7/09	Chest sepsis
						SAE2	9/7/09	Focal seizures
						SAE3	9/7/09	Cardiac arrhythmia
						SAE4	13/7/09	Increased urine output
						SAE5	13/7/09	Increased CRP
12	Addenbrooke's	53	F	13500	3/2/10	SAE1	3/2/10	IV line infection
						SAE2	3/2/10	Chest infection
						SAE3	7/2/10	Focal seizure
15	Salford	65	M	20900	10/2/10	SAE1	11/2/10	Ventilated acquired pneumonia

The events reported were felt, in the opinion of the Principal Investigator, to be expected in patients with subarachnoid haemorrhage and were not therefore attributed to the IMP. SAH is a life-threatening condition and although inclusion in the study excluded patients with concomitant

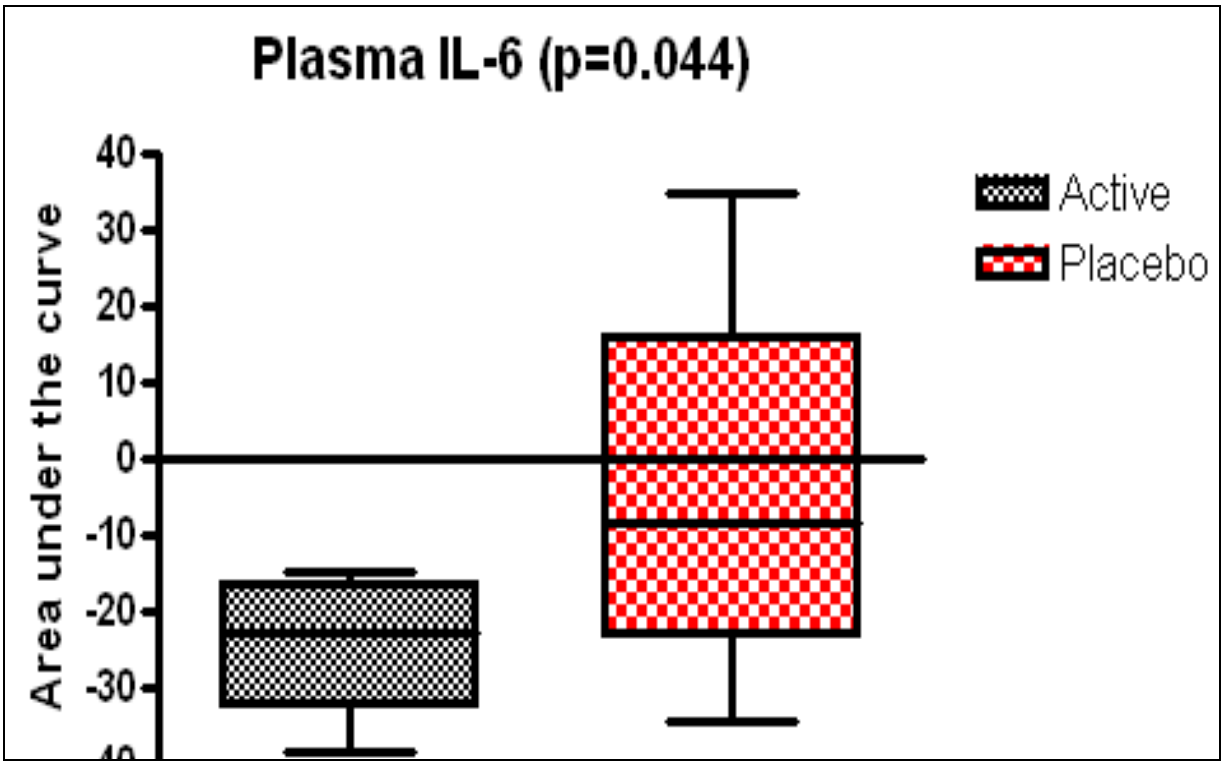
infections, the participants were pre-disposed to fluctuations in their clinical condition. In particular, patients with severe subarachnoid haemorrhages often require mechanical ventilation in an intensive care unit, pre-disposing them to systemic infection and sepsis. Additionally, patients requiring external ventricular drains are at risk of cerebrospinal fluid (CSF) infections. In this study, one patient developed a CSF infection (8% infection rate). This is considerably lower than the documented CSF infection rate within our department (approx 25 – 30% from the most recent audit) and this lower rate has been attributed to a meticulous aseptic technique. The lower infection rates in this and the previous dose-ranging study, has led to a change in clinical practice within our unit.

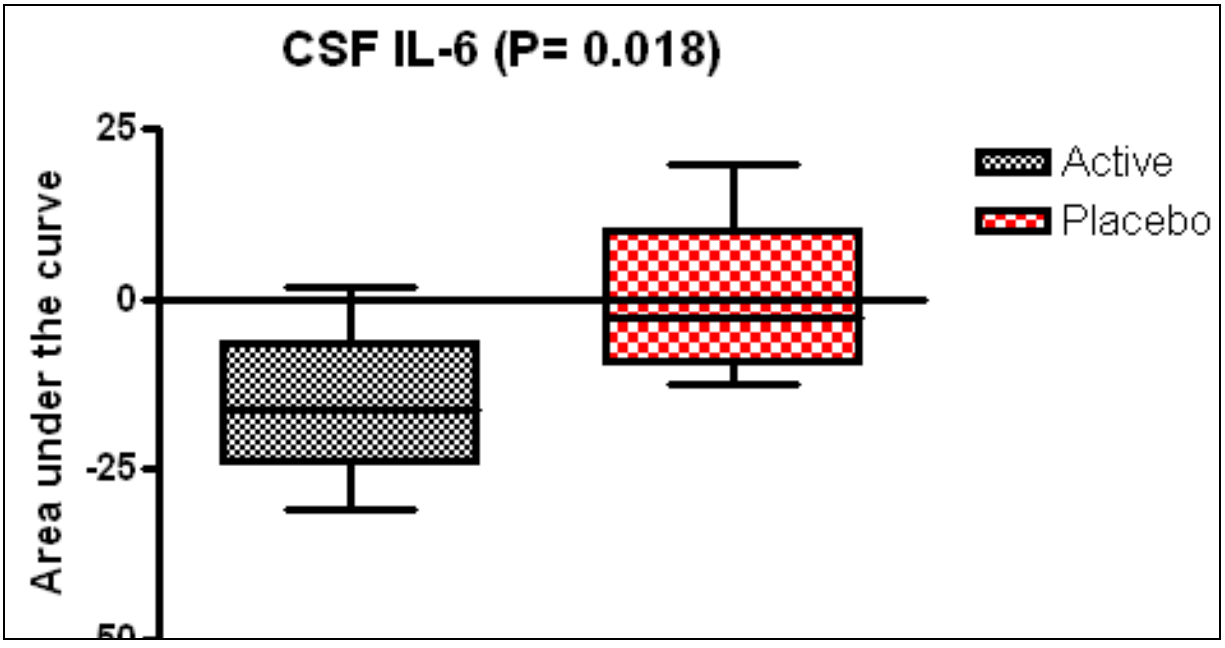
Trend analysis

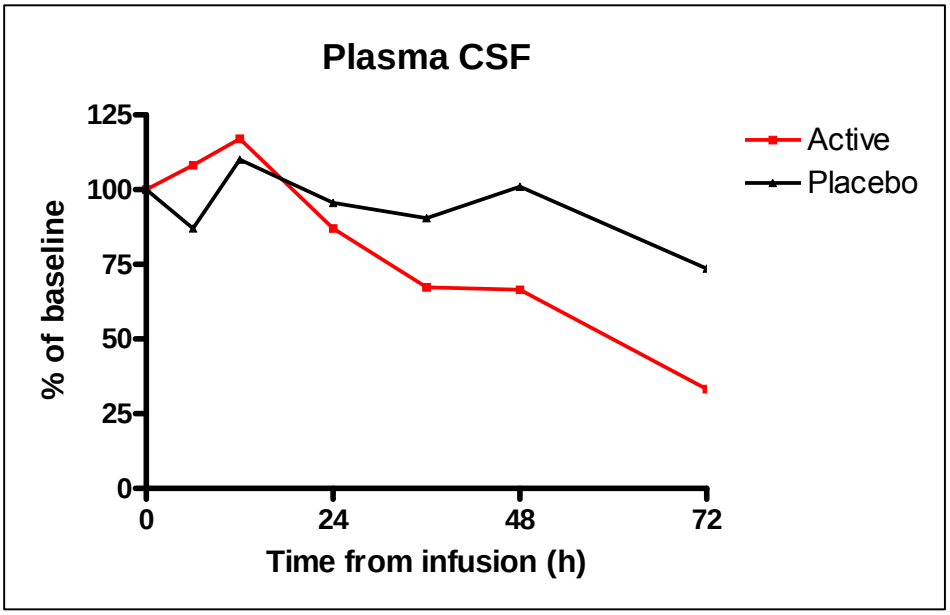
Infections	Chest (ventilated acquired pneumonia; chest infection)	3
	CNS infection	1
	Non-specific infection (increased CRP, IV line infection)	2
CNS events	Fluctuating GCS, focal seizure, raised ICP	4
Other conditions	Cardiac Arrhythmia	2
	EVD malfunction	1
	Increased urine output	1
	Desaturation (drop in oxygen concentration)	1
Total deaths (due to poor grade SAH)		0

Primary outcome

The primary outcome was to determine whether intravenously (iv) administered Kineret® caused a decrease in the concentration of central inflammatory biomarkers; interleukin-6 (IL-6) and C-reactive protein (CRP) following subarachnoid haemorrhage (SAH) compared to placebo. This was determined using the area under the curve (AUC) at 24h post infusion for IL-6 as well as other biomarkers. There was a significant decrease in IL-6 levels in both plasma and CSF at 24h in the Kineret® group and a non-significant decrease in plasma CRP in the Kineret® group at 72h. (See graphs below)


Plasma IL-6 (p=0.044)
Area under the curve
40
30
20
10
0
-10
-20
-30
Active
Placebo


CSF IL-6 (P= 0.018)
Area under the curve
25
0
-25
Active
Placebo



This report has been completed by Sharon Hulme, Research Manager; Mr Navneet Singh, Clinical Research Fellow under the supervision of the Chief Investigator, Dr Pippa Tyrrell and with the oversight of the study Sponsor, Salford Royal NHS Foundation Trust.