Final End of Study and Safety Report
Summary Adverse Event Log (27/11/07 – 18/12/08)

"An open labelled study of the cerebrospinal fluid pharmacokinetics of intravenous Kineret®
in patients with Subarachnoid Haemorrhage"

EudraCT number 2007-002337-36 **Main REC Ref No** 07/HO304/71

Final Report

Study title: An open-labelled study of the cerebrospinal fluid pharmacokinetics of intravenous Kineret® in patients with subarachnoid haemorrhage. **IL-1RA in SAH PK Study 2, EudraCT no**: 2007-002337-36 **REC Ref No**: 07/HO304/71

Funder: Medical Research Council

Chief Investigator: Dr Pippa Tyrrell

Local Investigators: Mr Andrew King (Salford), Mr Peter Hutchinson (Addenbrookes)

Study Sponsor: Salford Royal Foundation Hospital

Lead REC: Cambridgeshire 1 Ethics Committee
Date of Approvals from competent authorities: REC: 27/8/2008; MHRA 26/7/08
SSI: Salford and Trafford LREC and Cambridgeshire 2 LREC
Approval has also been obtained from the University of Manchester Senate Ethics Committee (5th October, 2007)

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

Study design: Dose-escalating study; five dosing regimes with five patients in each regime.

Safety reported to: Study Sponsor (SRFT)

Data and Safety review by: Independent Data and Safety Monitoring Committee (IDSMC) following completion of each regime and prior to further recruitment and dose escalation.

Recruitment plan: Patients with SAH, an EVD inserted for clinical reasons and who satisfied the inclusion and exclusion criteria were considered for recruitment into the study. The plan was to administer the IMP in up to 30 participants across the two research sites until the primary endpoint data (CSF and plasma concentrations at 30 minutes) for 25 patients (five in each of the five regimes).
Sites: Salford Royal Foundation Trust (Coordinating site); Cambridge University Hospitals NHS Foundation Trust (Addenbrooke's Hospital, collaborating site)

Recruitment commenced: Salford 1/10/07 Addenbrookes 1/12/07

Purpose of Study: To determine an administration regime that would achieve an experimentally effective IL-1RA concentration in CSF within a therapeutic time window. Secondary objectives were: 1) to define the dose relationship between central and peripheral concentrations of Kineret® and 2) to obtain further safety information in patients with SAH given IV infusion of Kineret®

Results

Patients screened: 88 (59 Salford: 29 Addenbrookes)
Participants recruited: 30 (24 Salford: 6 Addenbrookes)
Participants withdrawn: 5 (2 Salford: 3 Addenbrookes)

All participants receiving study drug completed the infusion. The three patients recruited from Addenbrooke have had data that was unsuitable for complete pharmacokinetic analysis. CSF concentrations of IL-1RA were occasionally 100 – 1000 fold those expected from our pharmacometric predictions. Following a thorough inspection by the study sponsor and the IDMSC, this was attributed to contamination of these CSF samples by Kineret® from plasma samples during on-site sample processing. There were 4 deaths during study period; all due to cerebral ischaemia. External Ventricular Drains (EVD) infection rate in the study cohort was 12%. This compared favourable to an overall departmental infection rate of 20% which was established by an independent audit performed during the same period. Apart from the aforementioned CSF samples from Cambridge patients, all 1L-1RA plasma and CSF concentrations in all regimes fell within predicted intervals calculated *a priori*. A 500 mg IV bolus followed by an IV infusion of Kineret® at 10 mg kg^{-1} h^{-1} achieved experimentally-therapeutic CSF concentrations of IL-1RA within 45 minutes.

Serious Adverse Events: 19* (16 Salford: 3 Addenbrookes) – All resolved
No SUSAR/SAR reported
Letter from IDSMC (26/1/09) with details of final review of data and safety enclosed

Breakdown of Events

ID	Site	Age	Sex	Total IMP Dose in mg	Date of IMP	AE number	Date of onset	Description of adverse event
1 (1A)	Salford	56	F	1300	27/11/07	AE 1	1/12/07	Pneumonia
2 (2A)	Addenbrooke's	59	F	1200	7/1/08	SAE1	8/1/08	Pneumonia
3 (3A)	Salford	64	F	1300	8/1/08	SAE1	14/1/08	DCI - Stroke
						SAE1	12/2/08	Chest infection
6 (6A)	Addenbrooke's	76	F	1100	17/3/08	SAE1	20/5/08	EVD malfunction
						SAE2		Pneumonia
8 (2B)	Salford	49	F	800	28/3/08	SAE1	7/4/08	CSF infection
9 (3B)	Salford	45	F	700	8/5/08	AE1	10/5/08	Pneumonia
						SAE1	14/5/08	Gastric infection
						SAE2	16/5/08	DCI
10	Salford	44	M	900	12/5/08	SAE1	16/5/08	CSF infection
12	Salford	71	M	800	16/6/08	SAE1	22/6/08	Cardiac arrthymias
						AE1	24/6/08	Rectal prolapse
						AE2	25/6/08	Chest infection
						AE3	25/6/08	Urinary tract infection
13	Salford	52	F	1100	18/6/08	SAE1	22/6/08	Chest infection
14	Salford	43	F	800	30/6/08	SAE1	6/7/08	Pyrexia of unknown origin
18	Salford	64	F	900	27/8/08	SAE1	3/9/08	Pyrexia of unknown origin
21	Salford	49	F	2100	23/9/08	AE1	25/9/08	Cardiac arrthymias
						SAE1	30/9/08	Vasospasm
22	Salford	56	M	2400	24/9/08	AE1	29/9/08	EVD malfunction
23	Salford	42	F	2200	26/9/08	SAE1	28/9/08	CNS infection
25	Salford	42	F	2300	10/11/08	SAE1	13/11/08	DCI
						SAE2	21/11/08	Chest infection
26	Salford	52	M	2300	12/11/08	SAE1	26/11/08	Pyrexia of unknown origin
27	Salford	67	M	3300	3/12/08	AE1	8/12/08	EVD malfunction
28	Salford	45	F	3300	8/12/08	SAE1	15/12/08	Chest infection

Summary breakdown of events

Infections	Chest (pneumonia; aspiration pneumonia)	9
	CNS infection	3 (including 1 before IMP given)
	Urinary Tract	1
	Gastric infection	1
	Pyrexia of unknown origin	3
CNS events	Stroke/Vasospasm/Delayed Cerebral Ischaemia	4
Other conditions	Cardiac Arrhythmia	2
	Exacerbation of rectal prolapse	1
	EVD malfunction	3
	Multi organ failure	1
Total deaths (due to stroke and poor grade SAH)		4