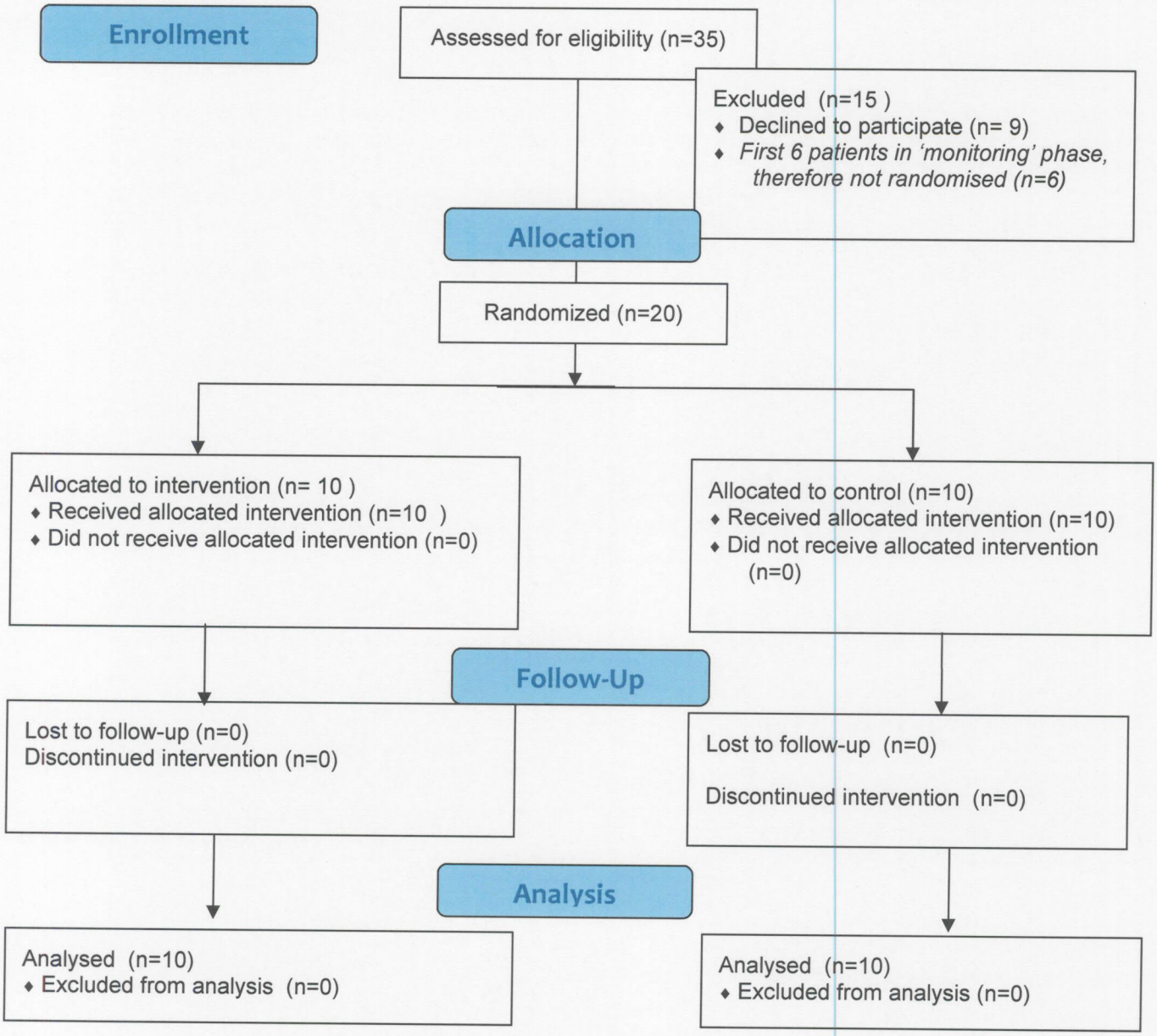
# END OF TRIAL REPORT

| **Trial Identification and Report Information** | |
|---|---|
| **Title** | A single centre phase II study of Interleukin 1 receptor antagonist in the treatment of severe Traumatic Brain Injury |
| **Chief Investigator:** | Mr Peter Hutchinson |
| **EudraCT no.:** | 2005-005707-42 |
| **REC Ref no.:** | 06/Q0108/64 |
| **R&D no.:** | A090624 |
| **Sponsor:** | Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge |
| **Sponsor's Address:** | Research & Development, Box 277, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Hills Road, Cambridge. CB2 0QQ |
| **Trial Statistician:** | Adel Helmy/ Dr Hugh Richards (now retired but involved in trial design and choice of statistics) |
| **Final Data Analysis carried out by:** | Adel Helmy |
| **Author of the report:** | Adel Helmy |


Enrollment
Assessed for eligibility (n=35)
Excluded (n=15 )
♦ Declined to participate (n= 9)
♦ First 6 patients in 'monitoring' phase, therefore not randomised (n=6)
Allocation
Randomized (n=20)
Allocated to intervention (n= 10 )
♦ Received allocated intervention (n=10 )
♦ Did not receive allocated intervention (n=0)
Allocated to control (n=10)
♦ Received allocated intervention (n=10)
♦ Did not receive allocated intervention (n=0)
Follow-Up
Lost to follow-up (n=0)
Discontinued intervention (n=0)
Lost to follow-up (n=0)
Discontinued intervention (n=0)
Analysis
Analysed (n=10)
♦ Excluded from analysis (n=0)
Analysed (n=10)
♦ Excluded from analysis (n=0)

| **Trial Summary** | |
|---|---|
| **Final Protocol version:** | IL1ra 02v4, version date 8 Sep 2008 |
| **Study Design:** | Single Centre Phase II Randomised Open Label Study of recombinant human IL1ra in Severe Traumatic Brain Injury<br><br>Interleukin-1 (IL-1) is a fundamental inflammatory cytokine that is involved in many pathophysiological processes, including co-ordination of the responses to inflammation and ischaemia (Allan et al). These effects are potentially protective but can also prove harmful, leading to tissue injury and death. The human body produces an endogenous antagonist called IL-1 receptor antagonist (IL-1ra) which has a highly specific action that selectively blocks the effects of IL-1 at its receptor. This remarkable finding has allowed the development of a synthetic version of IL1ra, called human recombinant IL1ra (hrIL-1ra). This agent has proved invaluable in studying the effects of IL-1 *in vitro* and *in vivo* and has recently been administered to patients with acute stroke. (Emsley et al).<br><br>Head Injury is a major cause of morbidity and mortality worldwide. Trauma is the leading cause of death in the first four decades of life with head injury being implicated in at least half the number of cases (American College of Surgeons 2004). Its burden extends from the individual to their family, friends and the wider community on both emotional and financial levels. In the UK, 1500 per 100,000 of the population (total 1 million) attend Accident and Emergency Departments with a head injury (Royal College of Surgeons of England 1999), 300 per 100,000 are admitted to hospital, 15 per 100,000 are admitted to neurosurgical units and 9 per 100,000 per year die from head injury (Jennett 1981, Hutchinson 1998).<br><br>When evaluating putative neuro-protective agents, a key step is identifying whether a drug reaches the desired target and whether this is at appropriate concentrations to act effectively. This study aims to provide this data for hrIL-1ra in traumatic brain injury and complements on-going studies in subarachnoid haemorrhage and stroke (Emsley 2005). This agent has been investigated extensively in animal models of brain injury and has been shown to reduce neuronal death (Allan 2005). A concentration of 100ng/ml was found to be effective in a rat model of ischaemic brain damage (Clark 2005). Recently, it has also been evaluated in stroke patients where clinical benefit has been demonstrated (Emsley 2005). However, in head injury, no studies investigating its pharmacokinetics, safety or efficacy exist.<br><br>When evaluating a novel agent in a new setting safety is a key consideration and all the evidence in the literature points to hrIL-1ra as a remarkably well tolerated agent. It has already been licensed for administration in rheumatoid arthritis as a 100mg daily subcutaneous injection (BNF 2005). Two studies in the mid 1990's evaluated the use of hrIL-1ra in severe sepsis in the intensive care setting. These studies showed rhIL-1ra to be safe in this patient population. The initial studies actually showed a survival benefit with rhIL-1ra (Fisher 1994) although this could not be replicated in multi-centre phase III trials (Opal 1997). Similarly, the stroke study investigating the neuroprotective role of rhIL-1ra showed it to be safe as well as efficacious (Emsley 2005). In all these studies, rhIL-1ra was administered intravenously (iv) with an initial 100mg iv bolus followed by an iv infusion of 2mg/kg/hr for 72 hours. This gives a much higher dose of the trial agent than that proposed in this study.<br><br>Microdialysis is a technique which enables the chemistry of the extracellular space to be sampled (Ungerstedt 1991, Hutchinson 2000). The principle is to place a fine catheter, lined with dialysis membrane and perfused with a physiological solution, into the tissue or organ of interest. Molecules diffuse from the extracellular space across the |

| | |
|---|---|
| | membrane into the solution which is then collected for analysis. Microdialysis is now well established as part of multimodality monitoring of patients with head injury in the Neuro-Critical Care Unit (NCCU). It has been shown to be a safe and effective monitor for measuring brain substrates (e.g. glucose), metabolites (e.g. lactate, pyruvate), neurotransmitters (e.g. glutamate, GABA) and drugs (e.g. chlormethiazole). In addition, pilot data from patients with severe head injury has been obtained showing that microdialysis can recover endogenous IL-1 and IL-1ra (paper in submission).<br><br>The first patient recruited to the study was on 13th October 2008 and the final follow up completed on the 27th December 2011, resulting in an overall study duration of 3 years 3 months. |
| **No. of participants:** | A total of 26 patients were recruited to the study: 6 patients in the monitoring phase of the study and 20 patients to the randomised phase. Randomisation was carried out by opening of sequential, numbered sealed envelopes allocating patients either to 'intervention' or 'control'. |
| **Investigational Medicinal Products:** | Recombinant Human Interleukin-1 Receptor Antagonist (Kineret®, Anakinra) 100mg subcutaneously once daily for 5 days.<br><br>In the original application, the Marketing Authorization holder was listed as Amgen Europe B.V. In Dec 2008, Biovitrum obtained an exclusive worldwide license to Kineret®. Biovitrum became Swedish Orphan Biovitrum in 2010. The change to the name of the Marketing Authorization Holder had not been communicated to the authorities in error. |
| **Date of End of Trial:** | Study end date 27th December 2011 |
| **Reported Serious Breaches:** | No Serious Breaches reported or identified during this study. |
| **Significant deviations identified during the trial:** | Although no Significant Deviations reported or identified during this study, we acknowledge there had been some deviations to the protocol:<br>.<br>- Section 4.44 xii stated "A data monitoring committee will be convened to ensure that the trial agent is administered in a safe and ethical fashion". This had not been set up;<br>- The 6 month follow up appointment from discharge have not always taken place at 6 months from the point of discharge. These have taken place to coincide with patients' visit to the clinic post discharge. |

| **Statistical Analysis and Main Findings** | |
|---|---|
| **Trial objectives and endpoints:** | Primary Objective:<br>To demonstrate the safety of rhIL1ra administered subcutaneously in Severe Human Traumatic Brain Injury.<br><br>Secondary Objectives:<br>To indentify the penetration of rhIL1ra into the brain extracellular space and the subsequent impact on clinical and biochemical markers in the head injury population as compared with placebo.<br><br>The trial objectives have not changed during the study and the data addresses the objectives as originally stated.<br><br>Primary endpoints:<br>1. Safety profile of rhIL-1ra administered subcutaneously.<br><br>Secondary endpoints:<br>1. Cerebral concentration of IL-1ra as recovered by microdialysis / CSF.<br>2. Other microdialysis / CSF markers |

| | |
|---|---|
| | –Metabolic markers: lactate, pyruvate, glucose<br>-Neurotransmitters: glutamate<br>-Cytokines:IL-1(alpha and beta), IL-6, IL-8<br>3. Multi-modality monitoring<br>-heart rate -invasive blood pressure monitoring<br>-intra-cranial pressure -arterial oxygen saturation<br>-arterial oxygen partial pressure -arterial carbon dioxide partial pressure<br>-arterial pH -core temperature<br>-brain tissue oxygen -brain temperature<br>4. Serum markers<br>-Full blood count -Urea and electrolytes<br>-C-reactive protein -Liver and bone function tests<br>-Peripheral IL-1ra, IL-1(alpha and beta), IL-6, IL-6, IL-8<br>5. GCS<br>6. Glasgow Outcome Score and SF-36<br><br>The trial endpoints have not changed during the study. |
| **Trial Analysis Population:** | All patients enrolled to the study were compliant with the protocol and completed all study assessments.<br><br>There were no changes to the trial analysis population during the study. |
| **Statistical Methods:** | Mulivariate projection methods were used to analyse the cytokine data. This was not stated *a priori* in the study protocol. We have published both the rationale and method for using these techniques in the peer reviewed literature. The original protocol envisaged using non-parametric tests for comparison of cytokine levels (Kolmogoro-Smirnov test to demonstrate the levels are not normal and the Wilcoxon Signed Rank Test for comparison between groups) however our statistical methods have developed in the intervening time and the original approach has been superseded. |
| **Results:** | IL1ra was safe in the study population with no adverse events attributable to the drug. There were 3 SAEs in the control group and 4 SAEs in the intervention group, non of which directly attributable to the IMP.<br><br>The monitoring phase demonstrated the utility of microdialysis in the recovery of a wide range of cytokines and chemokines from the human brain.<br><br>rhIL1ra penetrates the human brain following administration.<br><br>rhIL1ra modifies the inflammatory milieu following administration in the study population. *Manuscript in preparation.* |
| **Conclusion:** | The trial objectives have been addressed. We envisage a follow up larger phase 3 study of IL1ra in a larger group of patients with the drug administered at an earlier time point following injury to maximise the putative effects of the drug. |

| **Dissemination of Research Findings and Publications** | |
|---|---|
| **To participants:** | Given that the study has been completed we intend to contact all research participants and their General Practitioners by letter. These are enclosed in this submission. |
| **Publications:** | Helmy A, Antoniades CA, Guilfoyle MR, Carpenter KL, Hutchinson PJ. **Principal component analysis of the cytokine and chemokine response to human traumatic brain injury.** PLoS One. 2012;7(6):e39677. Epub 2012 Jun 22.<br>*Statistical methodology and demonstration of time variable nature of data*<br><br>Helmy A, Carpenter KL, Menon DK, Pickard JD, Hutchinson PJ. **The cytokine response to human traumatic brain injury: temporal profiles and evidence for cerebral parenchymal production.** *J Cereb Blood Flow Metab.* 2010 Aug 18. [Epub ahead of print] |

| | |
|---|---|
| | *Microdialysis methodology incorporating monitoring patients' data.*<br><br>The final manuscript detailing the study findings is currently being prepared. |

| **Chief Investigator's Signature** | |
|---|---|
| | Signature: PJA Hutchinson Date: 21-12-2012 |

**East Anglian Neurosurgery & Head Injury Service**
**Box 166**
**Secretary:** **01223 216780**
**Fax:** **01223 274645**

Addenbrooke's Hospital NHS
Cambridge University Hospitals NHS Foundation Trust

**Addenbrooke's Hospital**
Hills Road
Cambridge CB2 2QQ

Switchboard: 01223 245151
www.addenbrookes.org.uk

**Mr P J A Hutchinson BSc (Hons), MBBS, PhD, FRCS (Surg**
**Consultant Neurosurgeon**

Secretary: gillian.martin@addenbrookes.nhs.uk

Date

**PRIVATE & CONFIDENTIAL**

Address

Dear

**RE: IL1ra in Severe Traumatic Brain Injury**

I write to thank you for participating in a research trial while an inpatient in Addenbrooke's Hospital on the Neurosciences Critical Care Unit. We are completely reliant on the generosity and understanding of patients and families to carry out new research.

The study in which you took part has given us important information about how inflammation affects the brain after a head injury and has taken us one step closer to developing a new drug treatment for head injury. The drug was found to be safe (as has been proven in other previous trials) and it was able to get into the brain and change the inflammation within the brain. We are now hoping to carry out larger trials of the same drug to prove that it helps patients.

If you have any further questions about this trial please do not hesitate to contact me.

Kind regards.
Yours sincerely

Mr Adel Helmy
**Specialist Registrar in Neurosurgery**

**East Anglian Neurosurgery & Head Injury Service**
**Box 166**
**Secretary:** **01223 216780**
**Fax:** **01223 274645**

Addenbrooke's Hospital NHS
Cambridge University Hospitals NHS Foundation Trust

**Addenbrooke's Hospital**
Hills Road
Cambridge CB2 2QQ

Switchboard: 01223 245151
www.addenbrookes.org.uk

**Mr P J A Hutchinson BSc (Hons), MBBS, PhD, FRCS (Surg**
**Consultant Neurosurgeon**

Secretary: gillian.martin@addenbrookes.nhs.uk

Date

**PRIVATE & CONFIDENTIAL**

Address

Dear

**RE: IL1ra in Severe Traumatic Brain Injury**

I write to with regards to your patient who took part in a randomised control trial while an inpatient in Addenbrooke's Hospital. This was a phase II study of an anti-inflammatory drug, IL1ra (Anakinra,Kineret) in severe traumatic brain injury. Anakinra is already licensed in Rheumatoid Arthritis and is known to be safe at the dose used in the study.

The study is now closed and has demonstrated that Anakinra gets into the brain at a concentration sufficient to alter the inflammatory response to traumatic brain injury. The study findings are due to be published shortly.

Please do not hesitate to contact me should you require any further information.

Kind regards
Yours sincerely,

Mr Adel Helmy
**Specialist Registrar in Neurosurgery**