BLOC-ICH

Phase II trial of Interleukin-1 receptor antagonise in intracerebral haemorrhage: BLOcking the Cytokine IL-1 in ICH

NCT03737344

Statistical Analysis Plan

(Version 5.0, June 2021)

1. Roles and responsibility

Chief Investigator: ___ _____ Date: 3 Jun 2021

Trial Statistician: _____ _____ Date: 15 Jun 2021

2. Trial summary

Protocol: Version 2.0, 26-02-2021.

Design: Randomised, double-blind, placebo-controlled, multi-centre phase II trial.

Population: Adult patients with spontaneous, non-traumatic, supratentorial ICH.

Intervention: Masked recombinant human IL-1Ra (Kineret®) (manufactured as Kineret® from Swedish Orphan Biovitrum Ab (Sobi), Sweden). An initial 100 mg dose will be given subcutaneously (SC) within 8 hours of symptom onset, followed by 5 subcutaneous injections of 100mg Kineret, 12 hourly, for 72 hours.

Control: Matching placebo.

Randomisation: Stratified by centre and Glasgow Coma Scale (GCS) score at time of consent (6-13; 14 or 15).

Outcomes: Oedema extension distance (OED) at 72 ± 12 hours, early haematoma growth, Early Neurological Decline (END), clinical outcomes at 3 months, inflammatory biomarkers within four days, blood-brain barrier permeability at days 2-4.

Sample size: Target total recruitment of 80 participants (66 with primary outcome data). Early stopping, caused by pandemic and deemed unrelated to study progress or data, achieved 25 participants recruited.

3. Definitions

AuC	Area under curve
CRP	C-reactive protein
END	Early Neurological Decline
EQ-5D-5L	EuroQol 5-Dimension 5-level version
FSS	Fatigue Severity Scale
GCS	Glasgow Coma Scale
HADS	Hospital Anxiety and Depression Scale
IL-6	Interleukin-6
ICH	Intracerebral haemorrhage
mRS	modified Rankin scale
NIHSS	National Institutes of Health Stroke Scale
SIS	Stroke Impact Scale

4. Statistical principles

4.1 Confidence and significance levels

Analyses will be conducted using 95% confidence intervals. No formal adjustments will be made for multiplicity as there is a single primary analysis. Given small sample size, interpretation will be largely descriptive with no hypothesis testing.

4.2 Adherence

Adherence is defined as receipt of at least one dose of allocated intervention by participants who met the eligibility criteria. Details of, and reasons for, any participants who did not meet the eligibility criteria or did not receive at least one dose of their allocated intervention will be tabulated. Primary efficacy and safety analyses will include all participants who provided outcome data. Sensitivity analyses will include analysis of adherent participants only.

4.3 Interim analyses

Interim analyses were undertaken of recruitment and retention. No interim analyses of outcome data were presented to the Trial Management Team and no adjustment will be made for possibility of early stopping due to data monitoring considerations.

4.4 Timing of analyses

Clinical assessments and safety monitoring will take place at baseline, day 4 and day 30 post randomisation. An end of study assessment will be performed at 3 months (survival, mRS, SIS, FSS, EQ-5D-5L and HADS). Blood sampling is scheduled until study end. The research CT scan is scheduled for 72 ± 12 hours after symptom onset. Inflammatory biomarker data are scheduled at baseline and at days 1, 2 and 3. Adverse event checks are conducted up to day 30. No outcome analyses will be undertaken until the final three-month assessment has been completed and entered into the database.

4.5 Missing data

Missing baseline or outcome data will be sought.

The primary analysis will use a “complete case” approach. No imputation will be undertaken.

4.6 Software

Analyses will be undertaken in Stata version 14 or later.

5. Recruitment and retention

A CONSORT diagram will summarise participant recruitment and retention (see Appendix 1). Reasons for withdrawal and loss to follow-up will be tabulated by allocated intervention.

6. Baseline characteristics

Demographic and clinical data at baseline will be tabulated by allocated intervention. No statistical inference will be applied to these comparisons as the groups only differ by randomisation at this time-point. The following variables will be used to describe the groups:

Characteristic	Level	Intervention (N=***)	Control (N=***)
Age	Mean (SD) Minimum-Maximum		
Sex			
Male	N (%)		
Female	N (%)		
Ethnicity			
White	N (%)		
Mixed	N (%)		
Asian /Asian British	N (%)		
Black /Black British	N (%)		
Chinese	N (%)		
Other	N (%)		
Premorbid mRS			
0	N (%)		

1	N (%)		
2	N (%)		
3	N (%)		
4	N (%)		
5	N (%)		
Time between onset and arrival in hospital (hours)	Median (IQR) Minimum-Maximum		
Time between onset and drug admin (hours)	Median (IQR) Minimum-Maximum		
Blood Pressure at baseline	Mean (SD) Minimum-Maximum		
Pre-randomisaton Glasgow Coma Scale Score	Median (IQR) Minimum-Maximum		
Glasgow Coma Score Classification			
Mild	N (%)		
Moderate	N (%)		
Severe	N (%)		
NIHSS on admission/baseline – *how is this being categorised? I would suggest the following:*			
Minor (1-4)	N (%)		
Moderate (5-15)	N (%)		
Moderate-severe (16-20)	N (%)		
Severe (21-40)	N (%)		
Haematoma location			
Deep	N (%)		
Lobar	N (%)		
Uncertain	N (%)		
ICH volume	Median (IQR) Minimum-Maximum		
Intraventricular haemorrhage	N (%)		
Hypertension			
Yes	N (%)		
No	N (%)		
Type 1 Diabetes			
Yes	N (%)		
No	N (%)		
Type 2 Diabetes			
Yes	N (%)		
No	N (%)		
Atrial fibrillation			
Yes	N (%)		
No	N (%)		
Mechanical heart valve			

Yes No	N (%) N (%)		
Venous thromboembolism Yes No	 N (%) N (%)		
Use of antithrombotic drugs Aspirin Dipyridamole (Asasantin, Persantin) Clopidogrel Warfarin Sinthrome Rivaroxaban Apixaban Edoxaban Dabigatran Other	 N (%) N (%) N (%) N (%) N (%) N (%) N (%) N (%) N (%) N (%)		
Baseline Oedema extension distance	Median (IQR) Minimum-Maximum		

7. Outcomes

7.1 Oedema extension distance (OED)

After deriving the volume of perihaematomal oedema (PHO vol) and of the haematoma (ICH vol), the OED at 72 hours will be calculated using the formula:

$$r_h = \sqrt[3]{\frac{ICHvol}{\frac{4}{3}\pi}}$$

$$r_e = \sqrt[3]{\frac{PHEvol + ICHvol}{\frac{4}{3}\pi}}$$

$$OED = r_e - r_h$$

Primary analysis will be conducted under the principle of intention to treat and analysis of covariance will adjust for baseline value of OED.
Scans conducted between 48-60 & 84-96 hours will be included in the primary analysis.

7.2 Inflammatory biomarkers

Inflammatory biomarkers will be transformed using natural logarithm prior to analyses. The main outcome is the Area under Curve to Day 4 for $\log_e$(IL-6). The analyses will use linear regression to control for the baseline value of the analysed biomarker. Given the small sample size no adjustment will be attempted for the stratification criteria used in the randomisation process.

Where the value at a single time-point is missing, interpolation will be used to calculate the area under curve. Where more data are missing no imputation will be undertaken.

7.3 Clinical outcomes

Allocated groups will be compared on SIS, FSS, EQ-5D-5L and HADS using linear regression. The mRS will be dichotomised as 0 to 2 or 0 to 3, whichever threshold is nearer the median overall, and compared using binary logistic. The achieved sample size precludes the originally envisaged analyses using ordinal logistic regression and adjustment for stratification criteria.

7.4. Adverse events

The number of participants who experience infections, injection site reactions, hepatitis and rashes will be tabulated by allocated intervention and, if different, by intervention received. All other adverse events and serious adverse events will be tabulated by allocated intervention.

7.5 Sensitivity analyses

No additional sensitivity analyses will be undertaken.

Appendix 1 – CONSORT Diagram