Anakinra in the Treatment of Inflammation and Delirium in Orthopaedic Trauma and Repair (AnTIDOTe) Randomised Controlled Trial

Protocol version 0.01

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This protocol has regard for the HRA guidance and order of content

0.1 FULL/LONG TITLE OF THE TRIAL

Anakinra in the Treatment of Inflammation and Delirium Orthopaedic Trauma and Repair, a phase III, Bayesian Adaptive Randomised Controlled Trial in people aged over 65 presenting with fractured neck of femur.

0.2 SHORT TRIAL TITLE / ACRONYM

AnTIDOTe

0.3 RESEARCH REFERENCE NUMBERS

0.4 TRIAL REGISTRY NUMBER AND DATE

0.5 PROTOCOL VERSION NUMBER AND DATE

v0.1 7th July 2022

0.6 OTHER RESEARCH REFERENCE NUMBERS

0.7 SPONSOR / CO-SPONSORS / JOINT-SPONSORS

University of Manchester

0.8 FULL/LONG TITLE OF THE TRIAL

0.9 SHORT TRIAL TITLE / ACRONYM

0.10 PROTOCOL VERSION NUMBER AND DATE

0.11 RESEARCH REFERENCE NUMBERS

0.12 IRAS Number:

EudraCT Number:

ISRCTN Number / Clinical trials.gov Number:

0.13 SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature: Date: ……/……/…… Name (please print): Position:

Chief Investigator: Signature:
Date: ……/……/…… Name: (please print):

(Optional)

Statistician: Signature:
Name: (please print): Position:

0.14 Key Trial Contacts

Table 1: Key Contacts

Chief Investigator
Trial Co-ordinator
Sponsor
Join-sponsor(s) / co-sponsor(s)
Funder(s)
Clinical Trials Unit
Key Protocol Contributors
Statistician
Trials Pharmacist
Committees

0.15 LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EC	European Commission
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IMP	Investigational Medicinal Product

IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
NHS R&D	National Health Service Research & Development
NIMP	Non-Investigational Medicinal Product
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

0.16 TRIAL SUMMARY

Table 3: Trial Summary

Trial Title
Internal Ref. no. (or short title)
Clinical Phase
Trial Design
Planned Sample Size
Treatment Duration
Followup Duration
Objectives
Primary
Secondary
Outcomes
Primary
Secondary
Investigational Medicinal Products
Fomrulation, Dose, Route of Administration

0.17 ROLE OF TRIAL SPONSOR AND FUNDER

1 ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

1.1 Trial Management Committees

- Trial Steering Committee
- Data Monitoring (and ethics) Committee
- Trial Management Group

1.2 Protocol contributors

1.3 KEY WORDS: Insert relevant key words to describe the trial; no more than 6 phrases

1.4 BACKGROUND

1.5 RATIONALE

1.6 Assessment and management of risk

This trial is categorised as: (delete as appropriate)

2 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

2.1 Secondary objectives

2.2 Outcome measures/endpoints

2.3 Primary endpoint/outcome

2.4 Secondary endpoints/outcomes

2.5 Exploratory endpoints/outcomes

2.6 Table of endpoints/outcomes

Table 4: Trial outcomes

Objectives	Outcome measures	Timepoints
Primary Objective		

3 TRIAL DESIGN

4 TRIAL SETTING

5 PARTICIPANT ELIGIBILITY CRITERIA

5.1 Inclusion criteria

5.2 Exclusion criteria

6 TRIAL PROCEDURES

6.1 Recruitment

6.1.1 Participant identification

6.1.2 Screening

6.1.3 Payment

6.2 Consent

6.3 The randomisation scheme (if randomised trial)

6.3.1 Method of implementing the randomisation/allocation sequence

6.4 Blinding

6.5 Emergency Unblinding

6.6 Baseline data

6.7 Trial assessments

6.8 Long term follow-up assessments

6.9 Qualitative assessments

6.10 Withdrawal criteria

6.11 Storage and analysis of clinical samples (if details are provided in a laboratory/pathology manual there is no requirement to duplicate information in the protocol)

6.12 End of trial

7 TRIAL TREATMENTS

7.1 Name and description of investigational medicinal product(s)

7.2 Regulatory status of the drug

7.3 Product Characteristics

7.4 Drug storage and supply (if this included in a pharmacy manual then there is no requirement to duplicate information in the protocol)

7.5 Preparation and labelling of Investigational Medicinal Product

7.6 Dosage schedules

7.7 Dosage modifications

7.8 Known drug reactions and interaction with other therapies

7.9 Concomitant medication

7.10 Trial restrictions

7.11 Assessment of compliance with treatment

7.12 Name and description of each Non-Investigational Medicinal Product (NIMP)

8 PHARMACOVIGILANCE

8.1 Definitions

8.2 Operational definitions for (S)AEs

8.3 Recording and reporting of SAEs, SARs AND SUSARs

8.4 Responsibilities

8.5 Notification of deaths

8.6 Pregnancy reporting

8.7 Overdose

8.8 Reporting urgent safety measures

8.9 The type and duration of the follow-up of participants after adverse reactions.

8.10 Development safety update reports

9 STATISTICS AND DATA ANALYSIS

9.1 Sample size calculation

9.2 Planned recruitment rate

9.3 Statistical analysis plan

Aim: to fully describe the statistical analysis plan

9.3.1 Summary of baseline data and flow of patients

9.3.2 Primary outcome analysis

9.3.3 Secondary outcome analysis

9.4 Subgroup analyses

9.5 Adjusted analysis

9.6 Interim analysis and criteria for the premature termination of the trial

9.7 Participant population

9.8 Procedure(s) to account for missing or spurious data

9.9 Other statistical considerations.

10 DATA MANAGEMENT

10.1 Data collection tools and source document identification

10.2 Data handling and record keeping (If this information is included in a data management plan then there is no requirement to duplicate this information in the protocol)

10.3 Access to Data

10.4 Archiving

11 MONITORING, AUDIT & INSPECTION

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 Research Ethics Committee (REC) review& reports

12.2 Peer review

13.3 Public and Patient Involvement

12.3 Regulatory Compliance

12.4 Protocol compliance

12.5 Notification of Serious Breaches to GCP and/or the protocol

12.6 Data protection and patient confidentiality

12.7 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

12.8 Indemnity

12.9 Amendments

12.10 Post trial care

12.11 Access to the final trial dataset

13 DISSEMINIATION POLICY

13.1 Dissemination policy

14 REFERENCES