Interleukin-1 receptor antagonist treatment for refractory complex regional pain syndrome (INCA)

EudraCT number: 2021-000052-19

Sponsor Ref: UoL001571

Statistical Analysis Plan

Version 2.0 28/02/2024

	ORIGINATED BY	QC PERFORMED BY	APPROVED BY
Name	Ruth Knight	Aiswarya Anilkumar	Ruth Knight
Title	Lead Statistician	Statistician	Lead Statistician
Date	28/02/2024		
Protocol Version and Date	V6.0 21/11/2023		

1 Approval and Agreement

SAP Version Number being approved:2.0

Trial Statistician

Name Aiswarya Anilkumar

Signed* 

Date 16 Apr 2024

***Signature should be evidenced via physical signature (wet-ink or electronic).**

Senior Statistician

Name Michaela Brown

Signed* 

Date 18 Apr 2024

***Signature should be evidenced via physical signature (wet-ink or electronic).**

Chief Investigator/clinical lead

Name Dr Andreas Goebel

Signed* 

Date 16 Apr 2024

***Signature should be evidenced via physical signature (wet-ink or electronic).**

2 Table of Contents

3 Glossary

AR	Adverse reaction
AE	Adverse event
BPI	Brief Pain Inventory
CInv	Chief Investigator
CRF	Case report form
CRPS	Complex Regional Pain Syndrome
CTRC	Clinical Trial Reasearch Centre
CTU	Clinical Trials Unit
HADS	Hospital Anxiety and Depression Scale
IDSMC	Independent Data and Safety Monitoring Committee
IMP	Investigational medicinal product
IQR	Inter-quartile range
LCTC	Liverpool Clinical Trials Centre
NRS	Numerical Rating Scale
PHQ-9	Patient Health Questionnaire 9
QST	Quantitative Sensory Testing
SAE	Serious adverse event
SAR	Serious adverse reaction
SOP	Standard Operating Procedure
SD	Standard deviation
TSC	Trial Steering Committee
WOCBP	Women of child bearing potential

4 Roles and Responsibilities

Trial Statisticians: Miss R Cooper and Miss Anilkumar (Liverpool Clinical Trials Centre, University of Liverpool), Lead Statisticians: Dr R Jackson and Dr R Knight (Liverpool Clinical Trials Centre, University of Liverpool), Chief Investigator: Dr A Goebel (Clinical Sciences Centre, University Hospital Aintree)

Author's contributions

R Cooper and R Jackson proposed the statistical analysis plan. R Cooper drafted the SAP. R Jackson and A Goebel read, amended and approved the statistical analysis plan.

R Knight made updates to the SAP to reflect updates to the protocol. A Anilkumar and A Goebels reviewed these. R Knight and A Goebel approved the updated statistical analysis plan.

5 Statement of Compliance

This Statistical Analysis Plan (SAP) provides a detailed and comprehensive description of the pre-planned analyses for the study "INCA". The planned statistical analyses described within this document are compliant with those specified in brief within the INCA protocol v6.0 21/11/2023.

The purpose of the plan is to:

a. Ensure that all analyses are appropriate for the aims of the trial, reflect good statistical practice, and minimise bias by preventing inappropriate post hoc analyses.
b. Ensure that the analyses performed are consistent with the conditions of the protocol.
c. Explain in detail how the data will be handled, covariates derived and analysed to enable the analysis to be replicated, if necessary.

This study is carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996) amendments and will be conducted in compliance with the protocol, Clinical Trials Research Centre (CTRC) Clinical Trials Unit (CTU) Standard Operating Procedures (SOPs) and EU Directive 2001/20/EC, transposed into UK law as the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004.

6 Introduction

The interim analysis results will be described in a confidential Independent oversight committee report. The trial intervention name will be used as there is only one treatment for the INCA study and results presented 'Overall'.

The results of the final analysis described within this statistical analysis plan will be contained within a statistical analysis report. This report will be used as the basis of the primary research publications according to the study publication plan. Where analyses are presented which are not included in the SAP, justification as to their inclusion must be provided.

This study is a clinical trial of a medicinal product and is registered on the EudraCT database. The statistical analysis plan has been developed to support the posting of results on the EudraCT system. This is a regulatory requirement which should be fulfilled within 12 months after the end of the study as defined within the clinical trial protocol.

All analyses are performed with standard statistical software (SAS version 9.4 or later). The finalised analysis datasets, programs and outputs will be archived following Good Clinical Practice guidelines and SOP LCTC_GE018 Archiving Procedures in LCTC (Liverpool Clinical Trials Centre).

7 Background and Rationale

The full background and rationale for the trial can be found in the "Introduction and Rationale" section of the protocol. Complex Regional Pain Syndrome (CRPS) is a condition that causes chronic refractory and debilitating neuropathic pain in a limb affected by trauma. The exact pathophysiology of CRPS is still not fully understood. Anakinra is an IL-1 receptor antagonist that competes with IL-1 beta for its receptor. It has found use in a number of autoimmune inflammatory conditions such as juvenile arthritis.

No studies have been performed on using anakinra in CRPS. We propose initially a small feasibility study in a small cohort of patients using anakinra to determine tolerability and safety in refractory moderate to severe CRPS, prior to a larger randomised controlled trial. Anakinra is well known in its use in rheumatoid arthritis and periodic fevers and has a good safety profile in these conditions.

8 Objectives

The aim this research study is to assess the feasibility of performing a randomised controlled trial in patients with moderate to severe CRPS and to determine parameters for the design and power calculation of such study. Please refer to the "Objectives" section of the protocol for further details on the study objectives.

9 Study Design

9.1 Overall study design

INCA is a single arm feasibility open label study.

9.2 Blinding

INCA is an open label study, all researchers and participants know Anakinra is being administered to all patients.

10 Consent process

Prospective consent will be obtained following initial screening. Please refer to the "Informed Consent" section of the protocol for further details on the consent process.

11 Study population

11.1 Inclusion criteria

The inclusion criteria can be found in the "Inclusion Criteria" section of the protocol.

11.2 Exclusion criteria

The exclusion criteria can be found in the "Exclusion Criteria" section of the protocol.

11.3 Removal of participants from intervention or follow-up

The removal of participants from intervention or follow-up can be found in the "Invervention Discontinuation and Participant Discontinuation/Withdrawal" section of the protocol. Participants may discontinue treatment for reasons including, but not limited to:

- Patient-led i.e. request by the patient / legal representative / consultee
- Unacceptable toxicity (see protocol section "Safety Reporting" for AEs))

- Intercurrent illness preventing further treatment.
- CRPS symptom progression which requires discontinuation of therapy or results in inability to continue to comply with study procedures
- Pregnancy
- Death
- Clinician-led:
    - Any change in the participant's condition that justifies the discontinuation of treatment in the clinician's opinion.
    - Reasons of non-adherence or non-compliance with treatment or other trial procedures
    - Participant meets an exclusion criterion (either newly developed or not previously recognised)
    - Participant unable to receive Anakinra for >=7 days consecutively

Data to be collected at the time of discontinuation will include the following:

- Reason for discontinuation (if available)
- Any AEs
- Pain intensity score (NRS)

If a study participant is discontinued from the study early, an End of treatment CRF will be completed describing the reason for discontinuation.

Those who wish to withdraw from further follow-up will have the data collected up to the point of that withdrawal included in the analyses. The participant will not contribute further data to the study unless this is required by law (e.g. safety events).

12 Method of assignment to intervention

All participants will receive the same treatment in this feasibility study.

13 Schedule of assessments

All follow up visits will be scheduled from baseline (day 0) for 180 days, see "Schedule of assessments and follow up" section of the protocol.

14 Interventions

Each participant will receive Anakinra for 4 months in the form of a solution injection with a dose of 100mg or 2mg/kg if body weight is under 50kg. Further details are provided in the "Drug dosage and duration of treament" section of the protocol.

15 Listing of Outcomes

15.1 Primary outcome(s)

The proportion of patients with no serious or condition-specific AE's. Pre-determined potential condition-specific AE's include persistent pain at injection site (>1 week) of at least moderate intensity (≥5 on a 0-10 NRS scale) and increase in CRPS associated pain (>=2points NRS), ongoing for >1 month.

15.2 Secondary outcomes

To identify any barriers to patient recruitment and retention:

1. Monthly registration rate.
2. The proportion of patients completing the study - retention rate, and reasons for non-completion.

To obtain data that will enable a larger randomised controlled trial to be designed in the future:

3. Change of pain intensity measured on a 0-10 point NRS from baseline (0 day) to 4 months/120 days after completion of Anakinra administration. Pain intensity at 120 days is defined for the purpose of this study as a mean of the weekly scores and daily over the last month of drug administration. This is determined by calculating the results of the patient pain diaries.
4. CRPS severity score
5. Global assessment of change
6. Analgesic Medication use
7. EQ-5D 5L
8. Patient Health Questionnaire 9 (PHQ-9)
9. Brief Pain Inventory (BPI)
10. Hospital anxiety and depression scale (HADS)
11. Skin sensitivity measured by mechanical quantitative sensory testing (QST)
12. Limb Volume (Figure of 8)
13. Work status

16 Sample size calculation

A sample size of 30 has been estimated for this feasibility study. As this is a feasibility study, the sample size calculation can be difficult to determine. The results of the feasibility study will serve as data for sample size calculations for a further study. Additional details and references for the selected sample size are provided in the "Sample size" section of the protocol.

17 Study Framework

As this a feasibility phase II study, study outcomes are focused on safety/tolerability, recruitment and protocol/treatment adherence. Evaluations of further clinical/laboratory/quality of life measures are also performed to provide useful information to inform further study designs and sample size calculations. All outcomes will be summarised using appropriate summary measures.

18 Timing and Objectives of Analyses

18.1 Interim Reporting

18.1.1 Reports to Independent Oversight Committees

The Independent data and safety monitoring committee (IDSMC)/Trial Steering Committee (TSC) for INCA will review the conduct of the trial in terms of patient recruitment and safety/toxicity at regular intervals (at least annually). The primary endpoint will be presented in terms of the proportion of participant tolerating anakinra and the safety of anakinra in participants with refractory moderate to severe CRPS.

18.1.2 Assessments of progression criteria

See section "Progression criteria" of the INCA protocol. Assessment of the clinical trial progress will focus on the recruitment and safety of the study, which will be assessed by the IDSMC.

1. **Recruitment***. Initial recruitment rate of 0.5 participants each month per centre for the first 6 months from recruitment start.
2. **Safety****[1].For the first 10 registered participants, ≤3 reporting persistent pain (>1 week) at injection site of at least moderate intensity (≥5 on a 0-10 NRS scale) or substantial CRPS pain increase (≥2points NRS), ongoing for >1 month despite and from the time of pain-related treatment stop.
3. **Safety****. Consider stopping if ≥30% of study participants experience a serious adverse reaction (SAR).

4. **Recruitment and adherence****: At least 12 participants registered and ≥50% of registered participants completing their active treatment.
5. **Futility**. After 12 participants have been recruited and completed the 4 months treatment period, an average of no pain increase among completed participants (to visit 5 (120 day)) and at least one participant reporting at least 2 points of pain reduction on the NRS (rounded to the nearest whole number), both these criteria referring to the average pain recordings over the last two weeks before visit 5 (120 day) compared to baseline (0 day).

*Assessed 6 months from recruitment start. ** Assessed 12 months from recruitment start.[1]or later if it takes longer for 10 participants to be registered).

18.1.3 Formal Interim Analyses

No formal interim analyses of primary or secondary outcomes will be performed but analyses of the accumulating data (recruitment, protocol deviations, baseline characteristics, compliance, withdrawals, missing data and safety data) will be performed at regular intervals (at least annually) for review by an IDSMC. See Section 25.1 for further details.

18.2 Final Analysis

End of the trial will be defined as the date on which data for all participants are frozen and data entry privileges are withdrawn from the trial database, see the "End of Trial" section of the protocol.

19 Disposition of Participants

A CONSORT flow diagram [2] will be used to summarise the number of patients who were:

i) assessed for eligibility at screening
   a. eligible at screening
   b. ineligible at screening*
ii) eligible and registered
iii) eligible but not registered*
iv) received treatment
v) did not receive treatment*
vi) lost to follow-up*
vii) discontinued treatment*
viii) registered and included in the primary analysis
ix) registered and excluded from the primary analysis*

*reasons will be provided, see Section 19.1 for categories.

19.1 Screening, eligibility and recruitment

Screening logs will be summarised by site in a table as frequencies and percentages detailing:

i. the number of patients who were assessed for eligibility,
ii. those who met the eligibility criteria at screening (denominator i),
iii. those who did not meet the eligibility criteria at screening (denominator i),
iv. those who were eligible and consent was obtained (denominator ii),
v. those who were eligible but consent was not obtained (denominator ii),
vi. those that consented and registered (denominator iv)

Reasons for ineligibility will be summarised overall and by site in a table with the following categories:

a) No diagnosis of CRPS I or II according to the Budapset research criteria at the time of assessment for this study.
b) First documented diagnosis of Budapest CRPS by a healthcare professional less than 18 months or longer than 15 years before the screening assessment.
c) Pain intensity average is not 6 or greater on a 0-10 point NRS over a minimum of seven consecutive daily entries prior to baseline (0 day) visit, with no single value below 5.
d) Has not completed a previous course of appropriate specialised physiotherapy.
e) Has not had a poor response or intolerance to at least one anti-neuropathic pain medication such as tricyclic antidepressants or gabapentinoids.
f) If a woman of childbearing potential (WOCBP), unwilling to confirm the use of adequate birth control during the trial period unless pregnancy is impossible.
g) Fertile male patients unwilling to use contraception for the duration of therapy if sexually active with a female partner.
h) Under 18 years old.
i) Medical conditions that in the opinion of the study investigator would make it unsafe for participation or can adversely affect outcomes.
j) Co-existing pain that in the view of the study doctor may make assessment of outcomes related to refractory moderate to severe CRPS unreliable.
k) Ongoing relevant litigation where its conclusion is imminent during the course of the study.
l) Medical Contraindications to Anakinra such as moderate/severe or progressive renal impairment (CLCR < 60 ml/min or eGFR<60ml/min/1.73m^2 or end stage renal disease including dialysis), or hepatic impairment (defined as any value of transaminases, γ-glutamy

transpeptidase, or bilirubin greater than 2 times the upper normal limit) or hypersensitivity to Anakinra or any of its excipients or to E.coli derived proteins.

m) Previous use of Anakinra.

n) Current or recent (within 6 months) use of other immunosuppressants or biologics

o) Neutropenia defined as Absolute Neutrophil Count ($<1.5x10^9/l$).

p) Requirement to receive a live vaccine during the trial duration.

q) Active or latent Tuberculosis Infection .

r) HIV, Hepatitis B or C carrier.

s) Brittle asthma.

t) Active malignancy or malignancy within 2 years.

u) Ongoing alcohol or drug misuse at registration.

v) Psychiatric or other mental health disorder which in the opinion of the study investigator may interfere with successful study participation.

w) Commencing new therapy for refractory moderate to severe CRPS that may alter the outcome of the trial drug; this includes new pain management program treatment. Equally patients who have completed pain management program within the past 3 months.

x) Subject is pregnant or breastfeeding, inadequate birth control, or the possibility of pregnancy during the study.

y) Patients who have a spinal cord or dorsal root ganaglion stimulator whose average pain is less than 6 out of 10 when stimulator is on.

Frequencies will be presented along with percentages using all ineligible patients (iii) as the denominator.

Reasons for declined consent will be summarised overall in a table with the following categories:

a) Does not want to take IMP

b) Does not want to take part in research

c) Unwilling to provide a reason

d) Other reason*

Frequencies will be presented along with percentages using all patients where consent was not obtained (v) as the denominator. *Other free text reasons will be classified by the chief investigator (CInv) or delegated other.

Reasons for patients who provided consent not being registered will be summarised overall in a table with the following categories:

a) No delegated staff available

b) Other reason*

Frequencies will be presented along with percentages using all patients where consent was obtained but registration didn't occur (iv-vi) as the denominator. *Other free text reasons will be classified by the CInv or delated other.

A recruitment summary table will be presented showing the following for each centre: centre code, hospital name, dates site opened/closed to recruitment, dates of first/last registration and total number registered.

19.2 Post registration discontinuations

Withdrawal information is collected on the Withdrawal and End of Treatment CRF.

Withdrawals from the study will be presented as line listings detailing:

1. Date of registration
2. Date of discontinuation of follow up
3. Number of days in the trial (Date of discontinuation of follow up – date of registration (2-1))
4. Who made the decision to withdraw participant from trial:
    a. Clinician
    b. Participant
5. Reason and level for discontinuation:

    Clinician:

    a. Death
    b. Participant transferred to a non-participating centre
    c. Serious Adverse Event (SAE)
    d. Other reason (specify free text to be categorised by CInv or delegated other)

    Participant level of withdrawal:

    a. Withdrawal of consent for ALL further follow-up
    b. Withdrawal of consent for OPTIONAL part/s of the study

    Participant reason:

    a. Free text reason to be categorised by CInv or delegated other.

20 Protocol Deviations

Protocol deviations that will be reported are defined and specified as minor or major within the monitoring plan [v1.0 16/05/2022] for the trial.

Patients to be excluded from analysis populations need to be defined in the template "LCTC_ST003_TEMP5: Protocol deviations and analysis set definitions for final statistical analysis report" and agreed and approved prior to analysis.

The number and percentage (denominator as number of patients registered) of patients with each separate protocol deviation will be presented in this analysis report along with the number and percentage (denominator as number of patients registered) of patients with:

i. at least one major protocol deviation;
ii. at least one minor protocol deviation;
iii. at least one protocol deviation of any classification (minor or major).

These will also be summarised across site. No formal statistical testing will be undertaken.

21 Unblinding

Not applicable since INCA is an open-label study.

22 Analysis Datasets

22.1 Efficacy Analyses

The primary and secondary outcome analyses will be conducted on all registered participants and for whom the outcome(s) of interest have been observed/measured. Patients who withdrew consent for trial continuation will contribute outcome data up until the point of withdrawal unless the patients' specifically request that the data are not to be used. No imputations will be made.

The membership of the analysis set for each outcome will be determined and documented and reasons for participant exclusion will be given prior to analysis. Reasons may include missing data, loss to follow up.

A per protocol analysis will not be performed, instead the occurrence of each protocol deviation will be monitored and sensitivity analysis performed as appropriate with patients experiencing deviations

of concern removed. The sensitivity analysis will apply to a secondary analysis of the primary outcome only.

22.2 Safety Analyses

The safety analysis data set will contain all participants that are registered and commenced trial treatment (received at least one dose of Anakinra).

23 Baseline Characteristics

Descriptive statistics will be reported overall. Categorical data will be summarised by frequency and percentages with the denominator as the number registered. Continuous data will be summarised by mean, standard deviation (SD), median, inter-quartile range (IQR), minimum and maximum.

Patient demographics are to be summarised as follows from Form 1:Screening:

- Age (years)
- Age categorised for EudraCT
    - Adults (18-64 years)
    - From 65 to 84 years
    - 85 years and over
- Sex
    - Male
    - Female
- Ethnicity
    - Arab
    - Asian Other
    - Bangladeshi
    - Black African
    - Black Caribbean
    - Black Other
    - Chinese
    - Gypsey or Irish Traveller
    - Indian
    - Irish
    - Other ethnic group

  - Other mixed
  - Other white
  - Pakistani
  - White and Asian
  - White and Black African
  - White and Black Caribbean
  - White British
- Clinical chemistry/Hepatic functions tests*
  - Sodium
  - Potassium
  - Urea
  - Creatinine
  - Biblirubin
  - ALT
  - Alkaline Phosphatase
  - GGT
- Haematology Tests*
  - Full Blood count
  - Full Blood count differential
  - Neutrophil count
  - Neutrophil count result (10^9/L)

*All Clinical chemistry/Hepatic functions tests and Haematology Tests will be summarised with the categories Normal, Abnormal NCS and Abnormal CS as collected on the CRF (bar the Neutrophil count result which is numeric).

The below patient demographics are collected on both Form 1 Screening and Form 2 Baseline, summaries should be provided for Form 2 but if missing the value on Form 1 should be used:

Vital signs

- Height [cm]
- Weight [kg]
- Heart rate [bpm]
- Blood pressure [mmHg]

Limb volume

- Limb volume (Lower) [cm]

- Limb volume (upper) [cm]

Average pain score over last 24 hours:

- At baseline

Research blood samples:

- Consent to blood samples (Yes/No)
- Blood sample taken (Yes/No)

24 Compliance with Interventions

Exposure to treatment will be assessed by mean dose (mg) per participant. Dosing is once daily for a maximum of 120 days; the mean and median number of doses per participant over the treatment period (expressed as number of days treatment administered for) will be summarised.

Compliance of treatment will be captured by summarising the number of returned used syringes compared to non-used syringes.The number of syringes used is detailed on the Accountability Log. The number of syringes dispensed will also be summarised as detailed on the Accountability log.

Compliance will be further categorised as: more than expected (1 or more additional doses), less than expected (at least one fewer than expected) and as expected (exact number expected taken) according to the doses taken and expected.

25 Analysis of Outcomes

25.1 Interim Reporting

25.1.1 For reports to independent oversight committees

No formal interim analyses of primary or secondary outcomes will be performed but analyses of the accumulating data (recruitment, protocol deviations, baseline characteristics, compliance, withdrawals, missing data and safety data) will be performed at regular intervals (at least annually) for review by an IDSMC.

Recruitment will be summarised as stated in Section 19. The number of patients lost to follow-up, the number still being followed-up successfully and number who have completed follow up will be presented. Alongside the completeness of data collected in relation to primary and secondary outcomes as detailed in the trial protocol. A summary of baseline characteristics as stated in Section 23 will also be provided. Compliance to treatment (as defined in Section 24) and visits will be reported. Compliance for treatment will be split into the following 30 day timepoints for reporting to the IOC: day 30, day 60, day 90 and day 120.

The IDSMC will also review the progression criteria for the INCA study.

25.1.2 Assessment of progression criteria

25.1.2.1 Recruitment

The recruitment rate will be calculated across the first 6 months of trial overall and by site as:

[total number registered]/[number of months open to recruitment]

If the average recruitment rate per site per month is 0.5 or more this criteria has been met.

25.1.2.2 Safety

The frequency and proportion of participants, denominator used as the number registered, who have experienced the below will be summarised:

- persistent pain (greater than one week) at the injection site of at least moderate intensity (≥ 5 on a 0-10 NRS scale)
- a substantial CRPS pain increase of ≥ 2 points NRS, ongoing for more than 1 month despite and from the time of pain related treatment stop.
- SARs

The substantial pain increase will be calculated as: CRPS pain at day X – CRPS pain at day (X-30), where X is >30. Persistent pain will be derived from the pain dairies and adverse events. Both substantial pain increase and persistent pain are collected throughout the trial as Adverse events and are particularily asked about at each visit (see forms 5 – Telephone Follow up, 6 Follow up and 7 Final Telephone follow up). The yes/no response at each visit and the derived substantial pain increase/persistent pain will both be used to ensure all events are captured.

If 3 or less patients report persistent pain or substantial pain increase across the first 10 participants registered this criteria will have been met.

However, stopping will be considered if 30% or more of study participants experience an SAR in the first 12 months of recruitment.

25.1.2.3 Recruitment and adherence

Assessed 12 months after recruitment started the following will be reported:

- Number registered
- Number and proportion of those completing their treatment

To meet this criteria at least 12 paticipants should be registered and at least 50% of participants registered completing their active treatment.

25.1.2.4 Futility

The average CRPS pain over the 2 weeks prior to visit 5 (day 120) will be calculated using the Pain diaries days 106 to 119 whereby the average will be:

[the sum of the completed days 106 to 119]/ [number of completed entries].

The baseline pain score, ranging from 0 to 10, is collected on Form 4: Baseline as the average pain from CRPS over the last 24 hours. The average difference will be calculated as the average pain over the 2 weeks prior to visit 5 – baseline measure (day 0). The difference will then be classified for each participant as ≥ 2 points of pain reduction on the NRS (rounded to the nearest whole number) or less than 2 points of pain reduction on the NRS, including an increase in score.

After 12 participants have been recruited and completed 4 months treatment period the criteria is met if both of the below are met:

- An average of no pain increase among the completed patients
- At least one participant reporting at least 2 points of pain reduction on the NRS

25.1.3 Formal Interim Analysis

Not applicable.

25.2 Final Analysis

25.2.1 Levels of significance and multiplicity

As INCA is a feasibility phase II study, study outcomes are focused on safety/tolerability, recruitment and protocol/ treatment adherence, therefore, all outcomes will be summarised using appropriate summary measures.

25.2.2 Primary Outcome(s)

To determine the safety and tolerability of Anakinra in patients with refractory moderate to severe CRPS.

25.2.2.1 Derivation

This is defined as the proportion of patients with no serious or condition-specific AEs. Pre-determined potential condition-specific AEs are:

- Persistent pain at injection site (greater than 1 week) of at least moderate intensity (≥5 on a 0-10 NRS scale)
- Increase in CRPS associated pain (≥ 2points NRS), ongoing for >1 month.

Serious or condition-specific AEs are indicated on the following case report forms (CRFs) INCA Premature discontuation form, INCA Withdrawal form, Form 6: Follow up, Form 5: Telephone follow up and Form 7: Final telephone follow up. Further details of the events are collected on INCA Adverse Events form and INCA Serious safety event report form.

Patients will be classified as either having experienced at least one serious or condition-specific AE or experienced no serious or condition-specific AEs. The proportion of patients with no serious or condition-specific AEs will be defined as:

[total number of patients to have experienced no serious or condition-specific AEs]/[total number of registered patients].

25.2.2.2 Analysis

The proportion of patients with no serious or condition-specific AEs will be reported. For participants who experience at least one serious or condition-specific AE the total number and average number per participant of the following will be reported:

- serious AEs
- condition-specific AEs
- serious and/or condition specific AEs

A sensitivity analysis will be performed on the primary outcome to remove patients experiencing protocol deviations of concern from the analysis set. The protocol deviations of concern will be identified and agreed prior to final analysis.

25.2.3 Secondary Outcomes

i) To identify any barriers to patient recruitment and retention, and

ii) To obtain data that will in the future allow to design a larger randomised controlled trial.

25.2.3.1 Secondary Outcome 1: To identify any barriers to patient recruitment and retention

To identify any barriers to patient recruitment and retention the following wil be calculated:

1. Monthly registration rate.
2. The proportion of patients completing the study - retention rate, and reasons for non-completion.

25.2.3.1.1 Derivation

The monthly registration rate will be calculated as:

[the number of participants registered]/[the number of months of recruitment].

The retention rate will be calculated for day 120 and day 180 completion as:
[the number of participants to have completed* the study]/[the number of participants registered].
*Study completion is defined as completing the follow up visit 5 (at day 120) and telephone follow up 5 (at day 180) for completion at day 120 and day 180 respectively.

25.2.3.1.2 Analysis

The total number of participants registered, the total number of months of recruitment and the number of patients completing the study visits at day 120 and day 180 will be reported overall and by site.

The monthly registration rate and the retention rate will be reported overall and by site. Reasons for non-completion including withdrawal and safety reasons will be reported.

25.2.3.2 Secondary Outcome 2: To obtain data that will enable a larger randomised controlled trial to be designed in the future

To obtain data that will enable a larger randomised controlled trial to be designed in the future, the following will be assessed:

1. Change of pain intensity measured on a 0-10 point NRS from baseline (0 day) to 4 months/120 days after completion of Anakinra administration. Pain intensity at 120 days is defined for the purpose of this study a mean of the weekly scores and daily over the last month of drug administration. This is determined by calculating the results of the patient pain diaries.

2. CRPS severity score,
3. Global assessment of change,
4. Analgesic Medication use,
5. EQ-5D 5L
6. PHQ-9
7. BPI
8. HADS
9. Skin sensitivity measured by mechanical QST
10. Limb Volume (Figure of 8)
11. Work status

Table 25-1 details the timepoints and CRFs where each outcome measure is collected.

Table 25-1 Secondary outcome collection

Outcome	Timepoint (Days)	CRF
Pain intensity on 10-point NRS	0 120	Form 4: Baseline INCA CRPS Severity Score Pain diaries day 93 to 120
CRPS Severity score	0, 30, 60, 90, 120	INCA CRPS Severity Score Pain diaries
Global assessment of change	120	
Analgesic Medication use	0, 120	Concaminant medication use
EQ-5D 5L	0, 30, 60, 90, 120, 180	INCA EQ-5D 5L
PHQ-9	0, 30, 60, 90, 120	INCA PHQ-9 Questionnaire
BPI	0, 30, 60, 90, 120	INCA BPI
HADS	0, 30, 60, 90, 120	INCA HADS
Skin sensitivity measured by mechanical QST	0, 120	INCA Quantative Sensory Testing
Limb volume (figure of 8)	0 60, 120	Form 1: Screening Form 6: Follow up
Work status	0 120	Form 4: Baseline Form 6: Follow up

25.2.3.2.1 Change of pain intensity measured on a 0-10 point NRS from baseline (0 day) to 4 months/120 days after completion of Anakinra administration.

Pain intensity at 120 days is defined for the purpose of this study as mean of the weekly scores and daily scores over the last month of drug administration. This is determined by calculating the results of the patient pain diaries.

25.2.3.2.1.1 Derivation

The total weekly score will be calculated as the total NRS score per week for days 93 to 120 (last 4 weeks, inclusive of days 93 and 120) from the patient pain diaries. The mean of the total weekly scores (average weekly score) per patient will be calculated as:

[sum of total weekly scores for days 93 to 120 (inclusive)]/ 4.

The mean daily average over the last month per patient will be calculated as:

[sum of the scores for days 93 to 120 (inclusive)]/28.

The change in score will be the weekly and daily average at day 120 minus the baseline score. The baseline score is collected on Form 4: Baseline and is the average pain from CRPS over the last 24 hours at baseline.

25.2.3.2.1.2 Analysis

Continuous data will be summarised using mean, SD, median, IQR, maximum and minimum value. Summaries will be provided for:

- Baseline score
- Average weekly scores (days 93 to 120)
- Daily average over the last month (days 93 to 120)
- Change in scores for weekly and daily average at day 120 from baseline.

25.2.3.2.2 CRPS severity score

25.2.3.2.2.1 Derivation

The CRPS Severity score CRF collects the NRS pain score now and over the last 24 hours. The change in score will be calculated as the score at day 120 minus baseline score.

25.2.3.2.2.2 Analysis

Continuous data will be summarised as in Section 25.2.3.2.1.2. Summaries will be provided for:

- Baseline score
- Day 120 score
- Change from baseline.

Continuous summaries will also be provided for scores at day 30, 60 and 90. Profile plots will also be provided from baseline to day 120.

25.2.3.2.3 Global assessment of change

25.2.3.2.3.1 Derivation

Global assessment of change is collected at day 120 on the Patient Global Impression of Change form. Patients are asked the following question "How would you describe your overall status regarding your pain since starting treatment?", which has the following answers:

- Very much improved
- Much improved
- Minimal Improvement
- No change
- Minimally worse
- Much worse
- Very much worse

25.2.3.2.3.2 Analysis

The number of patients to complete the form will be reported. Categorical data will be summarised using frequencies and percentages at day 120 with the denominator being those who completed the question.

25.2.3.2.4 Analgesic Medication use

25.2.3.2.4.1 Derivation

Analgesic medication use is collected throughout the trial on the concomitant medications form and is indicated from the variable "Type of medication". Patients taking Analgesic medications as recorded on the Concomitant medications form as a start date on or before registration (and end date post-registration) will be classified as taking Analgesic medications at baseline. At day 120 patients with an 'ongoing' end date or end date after day 120 (start date pre-day 120) for Analgesic medications on the Concomitatnt medications form will be classified as taking Analgesic medications at day 120. Analgesic medication use at day 180 will be defined similarly with day 180 replacing day 120.

A patient will also be classified as prescribed Analgesic medications throughout the trial if any Analgesic medication has a start date between registration and day 120, this will also be summarised from registration to day 180.

25.2.3.2.4.2 Analysis

Categorical data for analgesic medication use will be summarised using frequencies and percentages at baseline and day 120 with the denominator as the number of patients registered and the number to reach day 120 (defined as attended Visit 5 Form 6 day 120). A summary of Analgesic medications prescribed throughout the trial will also be provided by the number of events (courses) and the number of patients. The percentage of patients to be prescribed the analgesic medication will be calculated using the denominator of the number of patients registered.

To compare analgesic medication use at baseline and day 120 a cross-tabulation will be provided with two percentages using the denominators of total number of patients in the category at baseline and day 120 i.e. row and column percentages.

Analgesic medication use at day 180 will be summarised in line with the above with day 180 replacing day 120.

25.2.3.2.5 EQ-5D-5L

25.2.3.2.5.1 Derivation

EQ-5D-5L is collected at baseline and day 30, 60, 90, 120 and 180. The total health score today is collected and ranges from 0 to 100. A patient will also classify their health on the day of completion for the following: Mobility, Self-care, Usual activities, Pain/Discomfort and Anxiety/Depression which have the following categorisations of problems/pain/anxiety/depression: no, slight, moderate, severe and unable/extreme.

Change from baseline for total health score will be calculated at day 120 and day 180 as:
Day 120 – baseline and day 180 – baseline.

25.2.3.2.5.2 Analysis

The number of patients to complete the EQ-5D-5L at each timepoint will be reported. Summaries will be provided as in 25.2.3.2.2.2, with day 180 and change from baseline to day 180 also provided. Continuous summaries will also be provided for scores at day 30, 60 and 90. Profile plots will also be provided from baseline to day 180.

25.2.3.2.6 PHQ-9

25.2.3.2.6.1 Derivation

PHQ-9 is collected at baseline and days 30, 60, 90 and 120. A total of 9 questions are responded to in regards to how often a participant is bothered by the problems over the last 2 weeks. These are scored as “Not at all” (0), Several days (1), More than half the days (2) and Nearly every day (3). The scores are then summed to create a total score.

The change from baseline total score will be calculated as the day 120 score – baseline score.

25.2.3.2.6.2 Analysis

The number of patients to complete the PHQ-9 at each timepoint will be reported. Summaries will be provided as in 25.2.3.2.2.2. Continuous summaries will also be provided for scores at day 30, 60 and 90. Profile plots will also be provided from baseline to day 120.

25.2.3.2.7 BPI

25.2.3.2.7.1 Derivation

BPI is collected at baseline and days 30, 60, 90 and 120. A total of 9 questions are responded to in regards to the pain experienced by each participant, questions 1,2, 7 and 8 will not be summarised. Questions 3 to 6 summarise the pain experienced by the participant:

- At its worst in the last 24 hours
- At its least in the last 24 hours
- On average
- Right now

Each category is score 0 to 10 as ‘No pain’ to ‘Pain as bad as you can imagine’.

Question 9 ask patients how, in the last 24 hours, pain interferes with:

- General activity
- Mood
- Walking ability
- Normal work (includes both work outside the home and housework)
- Relations with other people
- Sleep
- Enjoyment of life

Each category is score 0 to 10 as 'Does not interfere' to 'Completely interferes'. For question 9, the average pain interference score will be calculated using the mean of the 7 categories responded to.

25.2.3.2.7.2 Analysis

The number of patients to complete the BPI form at each timepoint will be reported. Summaries will be provided as in 25.2.3.2.2.2 for questions 3 to 6 and for the average pain interference score for question 9. Continuous summaries will also be provided for scores at day 30, 60 and 90. Profile plots will also be provided from baseline to day 120 for continuous data.

25.2.3.2.8 HADS

25.2.3.2.8.1 Derivation

The HADS questionnaire is completed at baseline and day 30, 60, 90 and 120. The questionnaire contains 7 anxiety and 7 depressions questions which answers are ranked 0 to 3 based on how the patient has felt the past week. The total anxiety and depression scores are calculated from the 7 responses and ranges from 0 to 21.

The change in score from baseline will be calculated as day 120 minus baseline score for both total anxiety and total depression score.

25.2.3.2.8.2 Analysis

The number of patients to complete the HADS form at each timepoint will be reported. Summaries will be provided as in 25.2.3.2.2.2 for anxiety and depression separately. Continuous summaries will also be provided for scores at day 30, 60 and 90. Profile plots will also be provided from baseline to day 120.

25.2.3.2.9 Skin sensitivity by mechanical QST.

Analysis to be performed by the Co-I.

25.2.3.2.10 Limb volume

25.2.3.2.10.1 Derivation

Limb volume is collected at Screening, day 60 and day 120 for both Upper and Lower Limb measured in cm. Change in limb volume will be summarised as volume at day 120 minus screening.

25.2.3.2.10.2 Analysis

Summaries will be provided as in 25.2.3.2.2.2 for upper and lower limb volume separately. A continuous summary of limb volume at day 60 will also be provided.

25.2.3.2.11 Work status

25.2.3.2.11.1 Derivation

Work status is recorded at baseline and day 120, with the following categories:

- Employed
- Self-employed
- Not working.

25.2.3.2.11.2 Analysis

Categorical data will be summarised using frequencies and percentages at baseline and day 120 with the denominator being those who completed the question at each timepoint.

To compare work status at baseline and day 120 a cross-tabulation will be provided with two percentages using the denominators of total number of patients in the work status category at baseline and at day 120 i.e. row and column percentages. A simiplified table of working (classified as employed or self-employed) and not working at baseline and day 120 will also be provided.

26 Safety Evaluations

All non-serious adverse events (AEs) and SAEs reported by the clinical investigator will be presented in a table (or non-serious adverse reactions (ARs) and SARs if the study does not capture unrelated AEs). The number (and percentage) of patients experiencing each AE/SAE will be categorised by severity (mild, moderate, severe). For each patient, only the maximum severity experienced of each type of AE will be displayed. The number (and percentage) of occurrences of each AE/SAE will be presented. No formal statistical testing will be undertaken.

27 Additional Analyses

No additional analysis planned.

28 Document History

Statistical Analysis Plan Version	Protocol Version	Section number(s) changed	Description of changes	Justification for changes	Date Implemented
V2.0	V6.0	1 Approval and Agreement 4 Roles and Responsibilities 5 Statement of Compliance 19.1 Screening, eligibility and recruitment	Signatories changed Additional contributors/ contributions added Protocol version number updated Inclusion and exclusion criteria updated	Reflect statisticians currently involved in trial Reflect who made the changes in the updated version Reflect version of protocol SAP relates to Reflect updates that have been made in the protocol	

29 References

29.1 Non-standard statistical methods

29.2 Data Management Plan

INCA Data Management Plan V1.0 14/04/2022

29.3 Trial Master File and Trial Statistical File

INCA Trial Master File

INCA Trial Statistical File

29.4 Other Standard Operating Procedures to be adhered to

LCTC_ST002: Generation of Random Allocation

LCTC_ST003: Production of Statistical Analysis Plans and Reports

LCTC_ST004: Quality Control of Statistical Programming

LCTC_ST005: Statistical Programmed Data Checks

LCTC_ST006: Creating and Maintaining a Trial Statistical File

29.5 Other references

1. Gamble C, Krishan A, Stocken D, et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. JAMA. 2017;318(23):2337–2343. doi:10.1001/jama.2017.18556
2. Eldridge S M, Chan C L, Campbell M J, Bond C M, Hopewell S, Thabane L et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials BMJ 2016; 355 :i5239 doi:10.1136/bmj.i5239