Synopsis of MINIMISE-Pilot

Name of Sponsor: University College London

Name of Finished Product: Mycophenolate mofetil

Name of Active Ingredient: 2-morpholinoethyl ester of MPA.

Title of Study: Mycophenolate in limited cutaneous systemic sclerosis

A randomised prospective open label pilot trial comparing mycophenolate mofetil with no immunosuppression in adults with limited cutaneous systemic sclerosis

Investigators: Prof Christopher Denton

Study centres:

Royal United Hospitals Bath NHS Foundation Trust, Bath, BA1 3NG, United Kingdom

Southmead Hospital - NORTH BRISTOL NHS TRUST, Bristol, BS10 5NB, United Kingdom

Darlington Memorial Hospital - County Durham and Darlington NHS Foundation Trust, Darlington, DL3 6HX, United Kingdom

Ninewells Hospital - NHS Tayside, Dundee, DD1 9SY, United Kingdom

Chapel Allerton Hospital - LEEDS TEACHING HOSPITALS NHS TRUST, Leeds, LS9 7TF, United Kingdom

Aintree University Hospital NHS Foundation Trust, Liverpool, L9 7AL, United Kingdom

Royal Free Hospital - Royal Free NHS Foundation Trust, London, NW3 2QG, United Kingdom

Manchester Royal Infirmary - Manchester University NHS Foundation Trust, Manchester, M13 9WL, United Kingdom

Salford Hospital - Northern Care Alliance NHS Foundation Trust, Manchester, M6 8HD, United Kingdom

Freeman Hospital - THE NEWCASTLE UPON TYNE HOSPITALS NHS FOUNDATION TRUST, Newcastle, NE7 7DN, United Kingdom

Royal Hallamshire Hospital - SHEFFIELD TEACHING HOSPITALS NHS FOUNDATION TRUST, Sheffield, S5 7AU, United Kingdom

New Cross Hospital - The Royal Wolverhampton NHS Trust, Wolverhampton, WV10 0QP, United Kingdom

Publication: n/a

Studied period: 21/12/2021 (date first enrolment) – 10/08/2023 (date of last completed)

Phase of development: phase II, feasibility study

Objectives: The primary objective of MINIMISE-Pilot was to assess recruitment feasibility and endpoint viability for an event-driven trial designed to have relatively infrequent visits that reflect normal follow up and management of lcSSc. This external pilot trial aimed to inform the design of a definitive double-blind placebo-controlled trial.

Our ultimate aim was to assess whether patients with lcSSc on MMF have a lower rate of development of important complications that reflect "clinical worsening" than patients not on immunosuppression and gauge our ability to recruit patients into the definitive trial. In addition, aimed to ask whether we can identify subgroups of lcSSc more likely to respond to MMF.

Methodology: The MINIMISE-Pilot trial is a multicentre, UK phase II randomised prospective open label pilot trial comparing mycophenolate mofetil (MMF) with no immunosuppression in adults aged 18 years or more with limited cutaneous systemic sclerosis (lcSSc).

The primary objective was to assess recruitment feasibility and endpoint viability for an event-driven trial, designed to have relatively infrequent visits that reflect normal follow up and management of lcSSc.

This pilot trial aimed to provide critical information for the development of a future definitive trial that could potentially transform lcSSc patient management and explore whether the immunosuppressive agent MMF can slow down disease progression.

TRIAL DESIGN

This was a standalone feasibility pilot to assess recruitment feasibility and endpoint validity. It was a randomised prospective open label trial which aimed to randomise 120 patients in 13 centres (or more) across the UK, receiving either MMF target dose of 2g for the duration of the study or no MMF (no immunosuppression). Randomisation used minimisation with a random element, to reduce predictability, balancing for ACA positivity and disease duration. The following stratifying variables were used:

1. ACA+ versus ACA-
2. Disease duration: up to 4 years (< 4) versus four years or more (>=4)
3. Recruitment site

All patients received background standard of care medical therapy for SSc related symptoms and were to be followed up until they reached primary endpoint (event of disease progression).

PRIMARY OUTCOMES

Feasibility outcomes:

- Recruitment rate (the proportion of eligible patients enrolled into the trial)
- Adherence to the study protocol (by participants and clinicians/research teams at sites)
- Proportion of participants intolerant to MMF who discontinue therapy
- Proportion of MMF participants who reduce their dose
- Proportion of MMF tablets taken

- Loss to follow up in each group (MMF and Control)
- Information to guide the design of the definitive double-blind placebo-controlled trial by providing data to:
    - Estimate the number of centres and the length of the recruitment period that will be required for the definitive double-blind placebo-controlled trial
    - Identify any barriers to recruitment
    - Assess the rate of withdrawal from treatment due to adverse events and the rate of loss to follow up
- Information to guide the design of the economic evaluation of the definitive double-blind placebo-controlled trial

Clinical outcomes:

- Time to clinical worsening of lcSSc defined as development of new clinically significant endpoint:
    - Progressive lung fibrosis
    - Pulmonary hypertension
    - Scleroderma renal crisis
    - Heart failure
    - Severe gut involvement causing malnutrition
    - Major vascular complications in the fingers such as gangrene
    - Mortality (of any cause)

Number of patients: 120 planned, 43 analysed

Diagnosis and main criteria for inclusion:
Participant Inclusion Criteria
1. Participants with lcSSc classified by the 2013 EULAR ACR criteria for limited cutaneous subset of SSc
2. Participants with less than 7 years disease duration from first non-Raynaud's manifestation of SSc
3. Participants aged 18 years or more (≥ 18 years) at screening visit
4. If women of childbearing potential, the participant must have a negative pregnancy test at screening and baseline visits
5. Negative viral screen for HIV, Hepatitis B and C
6. Ability to provide full informed consent
7. Registered with a GP practice in the UK
8. Participants must be willing to attend for follow up visits (at site or remotely) and to comply with study-related procedures.

Participant Exclusion Criteria
1. Having already developed a complication of SSc that requires initiation of MMF or an alternative major immunosuppressive drug for SSc such as methotrexate, cyclophosphamide or azathioprine
2. Treatment with methotrexate, cyclosporine A, azathioprine, mycophenolate mofetil (MMF), rapamycin, colchicine, D-penicillamine, within ≤ 4 weeks prior to the baseline visit date
3. Contraindication to MMF (e.g., active infection that would preclude MMF in judgement of investigator), or previous intolerance of MMF

4. Any clinical condition which the investigator considers would make the patient unsuitable for the trial
5. Pregnancy (or planned pregnancy during trial participation) and/or breastfeeding
6. Women of childbearing potential and male participants with a partner of childbearing potential not willing to use adequate contraception as described in section 6.3.1.4 for the duration of trial treatment and within the time points specified following last trial treatment.
7. Active chronic infection such as COVID-19, tuberculosis, pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria. Suitability for enrolment once the participant has recovered from infection will be based on Investigator judgment.
8. Infection history:
i. Hospitalisation for treatment of infection within ≤ 8 weeks of screening visit date
ii. Use of parenteral (IV or IM) antibiotics (antibacterials, antivirals, anti-fungals, or antiparasitic agents) within ≤ 4 weeks of screening visit date
9. Receipt of a live-attenuated vaccine within ≤ 12 weeks of screening visit date
10. Participants enrolled in any other interventional trial within ≤ 4 weeks of the screening visit date (co-enrolment in observational studies is acceptable)
11. Current drug or alcohol abuse or dependence, or a history of drug or alcohol abuse or dependence within ≤ 52 weeks prior to screening visit date.
12. Any of the following laboratory results at screening visit:
• Glomerular filtration rate (GFR) <60 ml/min/1.73m^2
• Absolute neutrophil count (ANC) < 1.6 x 10^9/l
• ALT or AST > 2 x ULN
13. Participants not willing or unable to attend the on-site screening visit.

Test product, dose and mode of administration, batch number: Mycophenolate Mofetil, target daily dose 2g, oral, sourced from generic hospital stock

Duration of treatment: Planned for treatment up to a duration of up to 96 weeks but trial terminated early. First patient randomised 08/12/2021, Last treatment 10/08/2023

Reference therapy, dose and mode of administration, batch number: Standard of care for lcSSc.

Criteria for evaluation: This was a feasibility study primary looking at recruitment rate and adherence to study protocol to inform a full trial with a similar study design.

Statistical methods: Descriptive statistics of baseline characteristics and reported adverse events.

Summary Conclusions:
The study was terminated early by the funder due to recruitment being below the level that would suggest feasibility of a future full trial using a similar study design. As a feasibility pilot the goal of the MINIMISE-Pilot had been achieved. A total of 43 participants were enrolled in the study before it was terminated. The recruitment target was 120 participants.

Results:

- No participants reported any clinical endpoints at any visit.
- The data indicate a high consent rate of 84.3%, with 43 out of 51 eligible patients consenting to participate.
- Serious Adverse Events (SAEs): Three patients (7%) reported at least one SAE. This included two patients (9%) in the control group and one patient (5%) in the MMF group. The SAEs reported were gastrointestinal disorders (1 on MMF), injury and procedural complications (1 on control), and musculoskeletal and connective tissue disorders (1 on control).
- Adherence to MMF: Adherence to MMF was generally high, with 19 participants (95%) being 100% adherent at Week 1, decreasing to 9 participants (64%) at Week 24.
- Baseline Characteristics: The average age of participants was 56.56 years, with a nearly equal distribution between the control and MMF groups. Most participants were female (83.72%) and of White British ethnicity (81.40%).

Impact of Termination: The early termination of the study means that definitive conclusions about the effectiveness and safety of MMF in lcSSc cannot be drawn. However, the data collected may inform the design of a future definitive trial.

Next Steps: Further analysis of the collected data will be conducted to guide the design of a larger, double-blind placebo-controlled trial. This future trial informed by the results and experience of MINIMISE-Pilot will aim to provide more conclusive evidence on the potential benefits of MMF for lcSSc patients.