ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: June 24, 2024

ClinicalTrials.gov ID: NCT05478018

Study Identification

Unique Protocol ID:	H-21039032
Brief Title:	Type 1 Interferon Induced Changes to Exercise Adaptations in Systemic Lupus Erythematosus Patients (LUPEX)
Official Title:	Type 1 Interferon Induced Changes to Exercise Adaptations in Systemic Lupus
Secondary IDs:	

Study Status

Record Verification:	June 2024
Overall Status:	Active, not recruiting
Study Start:	April 1, 2022 [Actual]
Primary Completion:	April 16, 2024 [Actual]
Study Completion:	September 1, 2024 [Anticipated]

Sponsor/Collaborators

Sponsor:	Rigshospitalet, Denmark
Responsible Party:	Principal Investigator Investigator: Malte Lund Adamsen [madamsen] Official Title: Principal Investigator Affiliation: Rigshospitalet, Denmark
Collaborators:	Copenhagen Lupus and Vasculitis Clinic, Center for Rheumatology and Spine Diseases, Rigshospitalet

Oversight

U.S. FDA-regulated Drug:	No
U.S. FDA-regulated Device:	No
U.S. FDA IND/IDE:	No
Human Subjects Review:	Board Status: Approved Approval Number: H-21039032 Board Name: The Scientific Ethical Committee at the Capital Region of Denmark Board Affiliation: The Scientific Ethical Committee at the Capital Region of Denmark Phone: +45 72 21 68 55 Email: kontakt@nvk.dk

Address:	Ørestads Boulevard 5, Bygning 37K, st. 2300 København S
Data Monitoring:	Yes
FDA Regulated Intervention:	No

Study Description

Brief Summary:	Investigating the physiological effects of the interferons type 1 and 2 (IFNs), and the cytokines Interleukin 6 (IL-6) and tumor necrosis factor (TNF) on the adaptive changes to exercise in patients with systemic lupus erythematosus (SLE). The investigators hypothesize that the pathogenic blockage of IL-6 signalling that occurs in SLE, will decrease the cardiac and metabolic adaptations to aerobic exercise, and this decrease can be related to the IFN signature. 55 patients was included in a 12-week investigator blinded 1:1 randomised high intensity aerobic exercise intervention study.
Detailed Description:	55 patients with SLE have been included and randomized in a 1:1 fashion to a 12 week high intensity interval training (HIIT) course or standard care. Randomization was stratified by sex. All patients will undergo baseline and followup testing including: VO2Max, Pulmonary Function, Capillaroscopy, OGTT, Blood Tests, Epigenetic Markers of IFN, TNF and IL-6 signalling, Echocardiography,DXA, Medical Examination, Acute Exercise Bout with blood tests during and after an exercise bout similar to the intervention. A subgroup of patients will be offered a 82-Rb Pet CT of the heart as opt-in. The exercise programme consists of 12 weeks of tri-weekly exercise bouts of 38-45 minutes, following warm-up subjects will undergo 4 sets of 4 minute high intensity exercise, measured as the pulse being above 85% of HRmax for more than half the time; and 3 minute low to medium intensity exercise between the high intensity sets, measured as the pulse being between 40 to 60% of HRmax.

Conditions

Conditions:	Systemic Lupus Erythematosus Interferon Deficiency
Keywords:	Cardiac adaptations Metabolic adaptations High intensity interval training Interleukin-6 signature Tumor necrosis factor signature Interferon signature

Study Design

Study Type:	Interventional
Primary Purpose:	Basic Science
Study Phase:	N/A

Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	Double (Investigator, Outcomes Assessor)
Allocation:	Randomized
Enrollment:	55 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Exercise The patients will be randomized to 12-week supervised exercise training intervention or no exercise training. The exercise training program includes three supervised sessions per week over a 12-week period. The program consists of high intensity endurance training on ergometer bicycles. The intensity will progress throughout the 12 weeks of training. The training consists of 10 minutes of warm up at 40-60% maximum heart rate (HRmax), followed by 25 minutes of high intensity interval training (4 bouts of 4 min at >85% HRmax interspaced by 3 minutes of low intensity training at 40-60% Hrmax) and finally a 3-10 min cool-down of 50% Hrmax	Behavioral: High Intensity Interval Training Supervised high-intensity interval training for 12 weeks three times per week Other Names: • Aerobic Exercise
No Intervention: Non-Exercise Control group, therefore no supervised exercise regime. Subjects are asked to not increase habitual exercise routines.	

Outcome Measures

Primary Outcome Measure:

1. Changes in maximal aerobic capacity (VO2max)
   Measured by VO2max test

   [Time Frame: 12 weeks]
2. Patient reported Fatigue
   measured by Fatigue Severity Scale Questionnaire (FSS)

   [Time Frame: 12 weeks]

Secondary Outcome Measure:

3. Y2K updated SLE disease activity (SLEDAI-2K) with the SELENA modifications
   Physician evaluated changes in measures of SLE on a scale of 0-105 encompassing symptoms from 9 organs, higher scores indicate increased disease activity.

   [Time Frame: 12 weeks]
4. Short Form (SF)-36 Health Survey (0-100)
   Patient reported outcome measures (PROMs), Possible scores range from 0 to 100, with higher scores representing better health status

   [Time Frame: 12 weeks]
5. Change in Epigenetic Expression related to IFN alpha
   Measured by mRNA analysis

[Time Frame: 12 weeks]

Other Pre-specified Outcome Measures:

6. Systemic Lupus Erythematosus Disease Activity Index 2000 Responder Index-50 (SRI-50)
   Itemized Physician evaluated changes in measures of SLEDAI-2K on a scale from 0-22 that account for partial improvements in condition, higher scores indicate increased disease activity.

   [Time Frame: 12 weeks]

7. Visual Analog Scale (VAS) of global disease by Physician (0-100%)
   Physician evaluated changes in measures of SLE (0-100% of line segment), higher scores equal higher disease activity (worse)

   [Time Frame: 12 weeks]

8. Visual Analog Scale (VAS) fatigue (0-100)
   Patient reported outcome measures (PROMs) , higher scores equal higher fatigue (worse)

   [Time Frame: 12 weeks]

9. Visual Analog Scale (VAS) pain (0-100)
   Patient reported outcome measures (PROMs), higher scores equal more pain (worse)

   [Time Frame: 12 weeks]

10. SLAQ - (range 0 -33)
    Patient reported outcome measures (PROMs), Possible scores range from 0 to 33, with higher scores representing more active SLE (worse)

    [Time Frame: 12 weeks]

11. SLE activity Visual Analog Scale - (1-10)
    Patient reported outcome measures (PROMs), Possible scores range from 1 to 10, with higher scores representing more active SLE

    [Time Frame: 12 weeks]

12. Proteinuria
    Measured by Dipstick in a semiquantitive manner with the following categories indicating increased concentration, negative, +/-, 1+, 2+, 3+, 4+.

    [Time Frame: 12 weeks]

13. Body composition - Total adipose tissue - Weight
    Measured by DXA Scan - fat(g)

    [Time Frame: 12 weeks]

14. Body composition - Total adipose tissue - Percentage
    Measured by DXA Scan - fat(%)

    [Time Frame: 12 weeks]

15. Body composition - Android adipose tissue - Weight
    Measured by DXA Scan - android fat(g)

    [Time Frame: 12 weeks]

16. Body composition - Android adipose tissue - Percentage
    Measured by DXA Scan - android fat(%)

    [Time Frame: 12 weeks]

17. Body composition - Gyneoid adipose tissue - Weight
    Measured by DXA Scan - Gyneoid fat(g)

    [Time Frame: 12 weeks]

18. Body composition - Gyneoid adipose tissue - Percentage
    Measured by DXA Scan - Gyneoid fat(%)

[Time Frame: 12 weeks]

19. Body composition - Total Lean Mass - Weight
Measured by DXA Scan - Muscle Mass(g)

[Time Frame: 12 weeks]

20. Body composition - Bone Mass Density - Weight/square-centimeter
Measured by DXA Scan - BMD(g/cm^2)

[Time Frame: 12 weeks]

21. Waist-To-Height Ratio
measured with tape measure

[Time Frame: 12 weeks]

22. Dynamic Spirometry - Forced Expiratory Volume at 1 second (FEV1) volume
Pulmonary function testing, FEV1 volume

[Time Frame: 12 weeks]

23. Dynamic Spirometry - Forced Expiratory Volume at 1 second (FEV1) Percent of expected
Pulmonary function testing, FEV1%

[Time Frame: 12 weeks]

24. Dynamic Spirometry - Forced Vital Capacity Volume
Pulmonary function testing, FVC Volume

[Time Frame: 12 weeks]

25. Dynamic Spirometry - Forced Vital Capacity - Percent of Expected
Pulmonary function testing FVC%

[Time Frame: 12 weeks]

26. Dynamic Spirometry Forced Expiratory Volume at 1 second (FEV1) by Forced Vital Capacity - Ratio
Pulmonary function testing, FEV1/FVC ratio

[Time Frame: 12 weeks]

27. Dynamic Spirometry Forced Expiratory Volume at 1 second (FEV1) by Forced Vital Capacity - Ratio - Percentage of expected
Pulmonary function testing, FEV1/FVC ratio %

[Time Frame: 12 weeks]

28. Dynamic Spirometry - Total Lung Capacity - Volume
Pulmonary function testing, TLC Volume

[Time Frame: 12 weeks]

29. Dynamic Spirometry - Total Lung Capacity - Percentage of expected
Pulmonary function testing, TLC%

[Time Frame: 12 weeks]

30. Dynamic Spirometry - Residual Volume - Volume
Pulmonary function testing, RV-Volume

[Time Frame: 12 weeks]

31. Dynamic Spirometry - Residual Volume - Percentage of Expected
Pulmonary function testing, RV%

[Time Frame: 12 weeks]

32. Dynamic Spirometry - Alveolar Volume - Volume
Pulmonary function testing, AV-Volume

[Time Frame: 12 weeks]

33. Dynamic Spirometry - Alveolar Volume - Percentage of expected
Pulmonary function testing, AV-%

[Time Frame: 12 weeks]

34. Dynamic Spirometry - Diffusing capacity for Carbon Monoxide - Volume
Pulmonary function testing, DLCOc-Volume

[Time Frame: 12 weeks]

35. Dynamic Spirometry - Diffusing capacity for Carbon Monoxide - Percentage
Pulmonary function testing, DLCOc-%

[Time Frame: 12 weeks]

36. Dynamic Spirometry - Carbon monoxide transfer coefficient - diffusing capacity per liter of lung volume
Pulmonary function testing, KCO-Volume

[Time Frame: 12 weeks]

37. Dynamic Spirometry - Carbon monoxide transfer coefficient - diffusing capacity per liter of lung volume - percentage of expected
Pulmonary function testing, KCO-%

[Time Frame: 12 weeks]

38. Oral glucose tolerance test
75g of glucose taken while fasting

[Time Frame: 12 weeks]

39. Peripheral Capillary Changes - Capillary Density
Measured by Nailfold Capillaroscopy by trained physician (score of 1-4, higher scores equal fewer capillaries)

[Time Frame: 12 weeks]

40. Peripheral Capillary Changes - Average Capillary Width (micrometers)
Measured by Nailfold Capillaroscopy by trained physician - Width Measured in μm

[Time Frame: 12 weeks]

41. Peripheral Capillary Changes - Average Capillary Length(micrometers)
Measured by Nailfold Capillaroscopy by trained physician - Length Measured in μm

[Time Frame: 12 weeks]

42. Peripheral Capillary Changes - Count of avascular areas
Measured by Nailfold Capillaroscopy by trained physician - Avascular Areas (1-4 higher scores indicate more avascular areas)

[Time Frame: 12 weeks]

43. Peripheral Capillary Changes - Capillary Disorganization
Measured by Nailfold Capillaroscopy by trained physician - Capillary Disorganization (1-4 higher scores indicate more avascular areas)

[Time Frame: 12 weeks]

44. Peripheral Capillary Changes - Microhemorrhages (average per finger)
Measured by Nailfold Capillaroscopy by trained physician - Microhemorrhages (avg per finger)

[Time Frame: 12 weeks]

45. Peripheral Capillary Changes - Bushy Capillaries (average per millimeter)
Measured by Nailfold Capillaroscopy by trained physician - Bushy Capillaries (average per millimeter)

[Time Frame: 12 weeks]

46. Peripheral Capillary Changes - Megacapillaries (average per millimeter)
Measured by Nailfold Capillaroscopy by trained physician - Megacapillaries (average per millimeter)

[Time Frame: 12 weeks]

47. Peripheral Capillary Changes - Meandering capillaries (average per millimeter)
Measured by Nailfold Capillaroscopy by trained physician - Meandering capillaries (average per millimeter)

[Time Frame: 12 weeks]

48. Peripheral Capillary Changes - Tortous capillaries (average per millimeter)
Measured by Nailfold Capillaroscopy by trained physician - Tortous capillaries (average per millimeter)

[Time Frame: 12 weeks]

49. Peripheral Capillary Changes - Other Findings
Measured by Nailfold Capillaroscopy by trained physician - Physicians comment

[Time Frame: 12 weeks]

50. Change in fasting total cholesterol, low-density lipoprotein (LDL)-cholesterol and high-density lipoprotein (HDL)-cholesterol (mmol/L). Following an overnight fast (10 hours)
blood samples are collected and processed by a trained laboratory technician and analysed according to standard procedures.monitors (AX3; Axivity, Newcastle upon Tyne, UK) for a 3 to 5 day period

[Time Frame: 12 weeks]

51. Change in triglycerides (mmol/L). Following an overnight fast (10 hours)
blood samples are collected and processed by a trained laboratory technician and analysed according to standard procedures.monitors (AX3; Axivity, Newcastle upon Tyne, UK) for a 3 to 5 day period

[Time Frame: 12 weeks]

52. left ventricular and atrial end-diastolic volume
measured by echocardiography

[Time Frame: 12 weeks]

53. global longitudinal strain
measured by echocardiography

[Time Frame: 12 weeks]

54. stroke volume
measured by echocardiography

[Time Frame: 12 weeks]

55. left ventricular ejection fraction
measured by echocardiography

[Time Frame: 12 weeks]

56. Left ventricular mass
measured by echocardiography

[Time Frame: 12 weeks]

57. coronary perfusion reserve
measured by echocardiography (& 82Rb-PET-CT)

[Time Frame: 12 weeks]

58. Myocardial blood flow
Measured by 82Rb-Pet-CT, on a subset of 40 participants

[Time Frame: 12 weeks]

59. Axial accelerometer-based physical activity monitors
Free-living physical activity is measured using axial accelerometer-based physical activity monitors (AX3; Axivity, Newcastle upon Tyne, UK) for a 3 to 5 day period

[Time Frame: 12 weeks]

60. Change in peripheral blood Adaptation to Acute Exercise Bout - Analyzed for High Sensitvity C-Reactive Protein
Analyzed for HS-CRP

[Time Frame: 12 weeks]

61. Change in peripheral blood Adaptation to Acute Exercise Bout - Analyzed for Il-6
Analyzed for Il-6

[Time Frame: 12 weeks]

62. Change in peripheral blood Adaptation to Acute Exercise Bout - Analyzed for sIL-6r
Analyzed for soluble Il-6-receptor

[Time Frame: 12 weeks]

63. Change in peripheral blood Adaptation to Acute Exercise Bout - Analyzed for Il-1
Analyzed for Il-1

[Time Frame: 12 weeks]

64. Change in peripheral blood Adaptation to Acute Exercise Bout - Analyzed for Il-10
Analyzed for Il-10

[Time Frame: 12 weeks]

65. Change in peripheral blood Adaptation to Acute Exercise Bout - Analyzed for IFNα
Analyzed for IFNα

[Time Frame: 12 weeks]

66. Change in peripheral blood Adaptation to Acute Exercise Bout - Analyzed for IFNγ
Analyzed for IFNγ

[Time Frame: 12 weeks]

67. Change in peripheral blood Adaptation to Acute Exercise Bout - Analyzed for hgb
Analyzed for hemoglobin

[Time Frame: 12 weeks]

68. Change in peripheral blood Adaptation to Acute Exercise Bout - Analyzed for plates
Analyzed for thrombocytes

[Time Frame: 12 weeks]

69. Change in peripheral blood Adaptation to Acute Exercise Bout - Analyzed for Na
Analyzed for sodium

[Time Frame: 12 weeks]

70. Change in peripheral blood Adaptation to Acute Exercise Bout - Analyzed for K
Analyzed for potassium

[Time Frame: 12 weeks]

71. Change in peripheral blood Adaptation to Acute Exercise Bout - Analyzed for Cl
Analyzed for chloride

[Time Frame: 12 weeks]

72. Change in peripheral blood Adaptation to Acute Exercise Bout - Analyzed for hct
Analyzed for hematocrit.

[Time Frame: 12 weeks]

73. Change in peripheral blood Adaptation to Acute Exercise Bout - Analyzed for Ferritin
Analyzed for ferritin

[Time Frame: 12 weeks]

74. Change in peripheral blood Adaptation to Acute Exercise Bout - Analyzed for leucocyte differential
Analyzed for Leukocyte Differential

[Time Frame: 12 weeks]

75. Change in Epigenetic Expression related to IFN Beta

Measured by mRNA analysis on PBMCs

[Time Frame: 12 weeks]

76. Change in Epigenetic Expression related to IFN Gamma
Measured by mRNA analysis

[Time Frame: 12 weeks]

77. Change in Epigenetic Expression related to TNF
Measured by mRNA analysis

[Time Frame: 12 weeks]

78. Change in Epigenetic Expression related to IL-6
Measured by mRNA analysis on PBMCs

[Time Frame: 12 weeks]

79. Dietary Changes - Energy intake (kJ/day)
Patient Reported by dietary diary

[Time Frame: 12 weeks]

80. Dietary Changes - carbohydrate intake (g/day)
Patient Reported by dietary diary

[Time Frame: 12 weeks]

81. Dietary Changes - lipid intake (g/day)
Patient Reported by dietary diary

[Time Frame: 12 weeks]

82. Dietary Changes - Protein intake (g/day)
Patient Reported by dietary diary

[Time Frame: 12 weeks]

83. Dietary Changes - Other intake (categorical)
Patient Reported by dietary diary

[Time Frame: 12 weeks]

84. Muscle Biopsy for epigenetic markers of inflammation and myokine signalling
Optional for Participants: mRNA expression of genes related to TNF, IL-6, IFN alpha, beta and Gamma signalling

[Time Frame: 12 weeks]

85. Muscle Biopsy for epigenetic markers of physical activity
Optional for Participants: NF-κB p65 DNA binding activity (ELISA), phosphorylated and total JNK, phosphorylated AMPK (p-AMPK) total AMPK (Western blotting).

[Time Frame: 12 weeks]

86. Muscle Biopsy for epigenetic markers of physical activity - NF-κB p65 DNA binding activity (ELISA)
Optional for Participants: NF-κB p65 DNA binding activity (ELISA) & NF-κB binding activity (Western blotting).

[Time Frame: 12 weeks]

87. Muscle Biopsy for epigenetic markers of physical activity - c-Jun N-terminal kinase
Optional for Participants: phosphorylated and total JNK,

[Time Frame: 12 weeks]

88. Muscle Biopsy for epigenetic markers of physical activity - AMP-activated protein kinase
Optional for Participants: phosphorylated AMPK (p-AMPK) total AMPK (Western blotting).

[Time Frame: 12 weeks]

89. Autonomic Nerve Function Test - Resting HR by Vagus(tm)
Resting heart rate measured by R-R intervals on 1-lead ECG

[Time Frame: 12 weeks]

90. Autonomic Nerve Function Test - Rise from supine ratio of RR by Vagus(tm)
Rise from supine ratio of R-R intervals on 1-lead ECG

[Time Frame: 12 weeks]

91. Autonomic Nerve Function Test - Expiration Inspiration ratio of RR by Vagus(tm)
Expiration/Inspiration ratio of R-R intervals on 1-lead ECG

[Time Frame: 12 weeks]

92. Autonomic Nerve Function Test - Valsalva Maneuver ratio of RR by Vagus(tm)
Valsalva Maneuver ratio of R-R intervals on 1-lead ECG

[Time Frame: 12 weeks]

Eligibility

Minimum Age:	18 Years
Maximum Age:	
Sex:	All
Gender Based:	
Accepts Healthy Volunteers:	No

Criteria: Inclusion Criteria:

- Age ≥ 18 years by inclusion.
- Able to provide informed consent.
- Diagnosed SLE and fulfilling the classification criteria for SLE based on the American College of Rheumatology/EULAR criteria (SLICC)

Exclusion Criteria:

- Health conditions that prevent participating in the exercise intervention determined by the Research Coordinator these include but are not limited to
  - Major bone fracture at inclusion
  - Significant myalgias exacerbated by physical exercise
  - Active infectious disease such as Covid-19
  - Severe symptomatic pleuritis or pericarditis
- Corticosteroid use > 10mg/day at baseline
- Diagnosed with diabetes mellitus by physician
- Pregnancy
- SLEDAI-2k (with the SELENA modifications to Proteinuria changes so as to not exclude patients with chronic proteinuria) > 10
- Contraindications to 82Rb-PET with adenosine stress (according to local guidelines at the Dept. of Clinical Physiology, Nuclear Medicine and PET, Rigshospitalet, which are in accordance with the recommendations of the European Association of Nuclear Medicine)

- Fever, myocarditis or endocarditis
- Previous heart transplantation
- Dysregulated atrial or ventricular tachyarrhythmias
- Severe chronic obstructive pulmonary disease with a FEV1 of less than 50% of predicted
- Second or third degree sinoatrial or atrioventricular block
- Active bronchospasm at the time of the scan
- Systolic blood pressure <90 or >200 mmHg at the time of the scan
- Treatment with theophyllin within 7 days of the scan

Contacts/Locations

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Sub-Investigator: Iben E Rasmussen, MSc

IPDSharing

Plan to Share IPD: Yes
Data obtained through this study may be provided to qualified researchers with academic interest in Systemic Lupus Erythematosus.

Data or samples shared will be coded, with no PHI included. Approval of the request and execution of all applicable agreements (i.e. a material transfer agreement) are prerequisites to the sharing of data with the requesting party.

Supporting Information:
- Study Protocol
- Statistical Analysis Plan (SAP)
- Informed Consent Form (ICF)
- Clinical Study Report (CSR)
- Analytic Code

Time Frame:
Data requests can be submitted starting 9 months after article publication and the data will be made accessible for up to 24 months. Extensions will be considered on a case-by-case basis

Access Criteria:
Access to trial IPD can be requested by qualified researchers engaging in independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA).

For more information or to submit a request, please contact Malte.Lund.Adamsen.02@regionh.dk, Soeren.Jacobsen.01@regionh.dk or Regitse.hoejgaard.Christensen@regionh.dk

URL:

References

Citations:

Links:

Available IPD/Information:

Documents

Study Protocol
Document Date: September 27, 2023
Uploaded: 06/24/2024 07:58

Statistical Analysis Plan
Document Date: June 24, 2024
Uploaded: 06/24/2024 08:01

Informed Consent Form
Document Date: February 14, 2022
Uploaded: 06/24/2024 08:02