ISRCTN17106427 https://doi.org/10.1186/ISRCTN17106427

Hereditary Sensory Neuropathy Serine trial (SENSE trial)

Submission date	Recruitment status	[X] Prospectively registered
28/02/2023	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
13/03/2023	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
05/06/2026	Nervous System Diseases	[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Hereditary Sensory Neuropathy Type 1 (HSN1) is a rare genetic neuropathy which causes pain, sensory loss and variable weakness in the upper and lower extremities for which there is no current treatment.

We plan to perform a 12-month double-blind placebo-controlled trial of L-serine in patients with HSN1 due to mutations in the SPTLC1 or SPTLC2 gene.
The purpose of this study is to assess whether L-serine is an effective drug treatment to slow or stop disease progression in HSN1 due to mutations in the SPLTLC1 or SPTLC2 gene. The other aim is to assess if Magnetic Resonance Imaging (MRI) can accurately detect the changes (fat accumulation in muscle) which occur in the lower limb muscles of people who have HSN1.
We hope that the results will help us to confirm that MRI is an adequate measure to detect changes in the muscles of HSN1 patients.
A pilot study of L-serine HSN1 has shown it is safe and led to a mild improvement but was too small to say if L-serine treatment was effective.

Who can participate?
Adults aged 18 years or older diagnosed with HSN1 due to a mutation in either the SPTLC1 or SPTLC2 gene.

What does the study involve?
You will be in this study for approximately 12 months. Participation will involve 5 visits in total: 4 in-person visits and one telephone call. During some visits patients will complete questionnaires and have blood samples, MRI and nerve conduction studies. Skin biopsies may be performed.

Visits will be conducted at the Queen Square Centre for Neuromuscular Diseases, National Hospital for Neurology and Neurosurgery, London.

Participants will receive either L-serine OR placebo –treatment will be decided by chance and at random. The placebo contains no L-serine and no active drug of any type but it looks and tastes the same as L-serine.

Some people will not be eligible to be in the study or parts of the study, for example, if there is a reason they cannot safely have an MRI scan (e.g. metallic implants or fragments, or claustrophobia), they are planned to have foot surgery during the period of the study, they have diabetes or kidney stones, or if they are pregnant, breastfeeding or planning a pregnancy. Female participants of childbearing age will be asked to use contraception during the study period.
This is a double-blinded study which means that neither participants nor the doctor will know which treatment group participants are in. However, the doctor will be able to find out which treatment group participants are in if required (e.g. for a medical emergency).

What are the possible benefits and risks of participating?
Benefits:
The results of a similar smaller study in patients with HSN1 have shown that L-serine supplementation was promising in slowing disease progression. We hope to answer this question definitively with our study. Equally we hope that the results from the study will help us to better understand HSN. The information we get from this study may help us to treat this condition in the future and to share accurate information with other doctors and patients.
Risks:
Trial drug: L-serine is a supplement and has been used in other trials involving human participants and has been proven to be safe and well tolerated. Possible side effects may include nausea, vomiting, eye movement changes, startles to loud noises and brief, involuntary muscle twitching. These side effects have been noted in studies where patients have taken L-serine at higher doses than what will be used in this study, therefore it is thought to be unlikely that participants will experience them. Participants will be given a diary during the course of the trial to record any symptoms or possible side effects they have experienced. When coming for hospital visit, the doctor will also ask about any side effects participants have experienced.

Patient Reported Outcome Measures (Patient questionnaires): Occasionally some individuals may find some questions upsetting.
Lower limb MRI: MRI is a safe and generally well tolerated procedure. Participants who are pregnant or planning a pregnancy or have magnetic metal in the body will not be able to have MRI. There is no exposure to X-ray or harmful forms of radiation. The MRI machine is fairly noisy (ear protection is provided) and some people find the procedure slightly claustrophobic.
Blood Test: Blood tests do not pose a significant risk. At the site where the blood is taken brief discomfort might be experienced. There is a small risk of bruising, bleeding, fainting, and a very small risk of infection if the skin is broken. Bloods will be drawn by a trained health care professional and the utmost care will be taken to avoid these risks.
Skin Biopsies: Two tiny samples of skin will be taken from the side of the thigh after an injection of local anaesthetic. The risks include: feeling sick or lightheaded, bleeding, infection or scarring at the site of the procedure, discomfort or stinging from the procedure or the local anaesthetic lasting a few seconds. If participants have a known allergy to lidocaine (local anaesthetic used), alternative local anaesthetics will be chosen or participants will be excluded from the skin biopsy.
Nerve Conduction Studies: This test will examine the electrical function of the nerves in the arms and/or legs using surface sticky pads. Mild discomfort may be briefly experienced during performance of nerve conduction studies. It is an unusual feeling, and some people find them a little uncomfortable. They will be performed by a trained doctor. Testing will be discontinued at any point if participants feel distressed.
Incidental Findings: It is possible that, during the study, another medical condition (known as an incidental finding) could be detected during the clinical assessment or MRI scan. If this happens, participants will be informed and any required referrals, investigations and/or treatments will be arranged as we would in routine clinical practice.
Other risks: There are no other immediate risks in taking part in the study. There may be risks

involved in taking part in the study that are not known to the researchers at this time. If new risks are identified during the study, participants we will made aware of these. Participants will always be free to withdraw from the study without giving a reason.

Where is the study run from?
National Hospital for Neurology & Neurosurgery (UK)

When is the study starting and how long is it expected to run for?
March 2023 to September 2025

Who is funding the study?
Charcot-Marie-Tooth Association (UK)

Who is the main contact?
Dr Caroline Kramarz, c.kramarz@ucl.ac.uk

Contact information

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Clinical Trials Information System (CTIS)
2022-002567-30

Integrated Research Application System (IRAS)
1006207

Central Portfolio Management System (CPMS)
55711

Protocol serial number
148491

Study information

Scientific Title
Randomised double blind placebo controlled trial of L-serine in Hereditary Sensory Neuropathy type 1

Acronym
SENSE

Study objectives
The hypothesis underlying this study is that that L-serine is an effective treatment to slow or stop disease progression in HSN1 secondary to SPTLC1/2 mutations.
Mutations in SPTLC1 and SPTLC2 have been shown to cause the neuropathy by a gain of function mechanism as mutations alter the substrate specificity of serine palmitoyl transferase (SPT) whereby alanine and glycine are preferred over the canonical serine which results in the production of deoxysphingolipids (DSBs) which are neurotoxic.
Both transgenic mice expressing mutant SPTLC1 and HSN1 patients have elevated DSBs. Suppression of DSB production in HSN1 mutant HEK293 cells with increasing concentration of L-serine in the media indicated that the DSB production could in theory be overcome by increased systemic availability of L-serine. A treatment trial of L-serine in transgenic mice over-expressing SPTLC1 (C133W) reduced the DSB levels and improved the neuropathy and a pilot study of L-serine treatment in HSN1 patients showed promising results. We also gathered further evidence that DSBs are neurotoxic by using two preclinical models i.e., cultured mouse motor and sensory dorsal root ganglion neurones and human induced pluripotent stem (IPS) cell-derived sensory neurones. and showing that the DSBs are neurotoxic in these models.
Induced pluripotent stem cells (iPSCs) from HSN1 patients were also used to determine whether endogenous DSBs are neurotoxic, to understand the patho-mechanisms of toxicity and to assess response to serine therapy. HSN1 iPSC derived-sensory neurons demonstrated increased DSB production. Complex gangliosides (which are essential for membrane micro-domains and signalling) were reduced and neurotrophin signalling impaired, resulting in reduced neurite outgrowth. In HSN1 myelinating cocultures, we detected a major disruption of nodal complex proteins after 8 weeks, which led to complete myelin breakdown after 6 months. L-serine supplementation of these human iPSCs sensory neuron cultures markedly reduced DSB production and could significantly improve axon outgrowth and myelination, supporting its use as a rational therapy. By combining our preliminary studies together with the previous

transgenic mice L-serine treatment trial and the pilot US clinical trial, we feel there is now sufficient evidence to justify a definitive clinical trial of L-serine in patients with HSN1 secondary to SPTCL1/2 mutations.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 28/02/2023, London - Hampstead REC (Temple Quay House, 2 The Square, Bristol Research Ethics Committee Centre, BS1 6PN, UK; +44 2071048189; hampstead.rec@hra.nhs.uk), ref: 23/LO/0114

Primary study design
Interventional

Study design
Double blind placebo controlled clinical trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Hereditary sensory neuropathy type 1 HSN1A (HSAN1A) and HSN1C (HSAN1C)

Interventions
Patients will be randomly assigned to either receive L-serine or placebo in a 1:1 L-serine:placebo ratio.

Following participant consent and confirmation of eligibility, at visit 1, participants will be randomised at a ratio of 1:1 into a treatment group with L-serine and a placebo group using randomly varying block sizes.

Participants are considered to be enrolled into the trial following: consent, pre-treatment assessments, confirmation of eligibility, completion of the registration/randomisation process, allocation of the participant trial number and treatment by the remote system.

Trial medication: proposed dose of 400mg/kg of L-serine (total daily dose); dosage: three times daily for 12 months; administration: powder form to be dissolved in water.
Placebo medication: Dextrose monohydrate powder; dosage as above.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
L-serine

Primary outcome(s)

Difference in lower limb muscle fat fraction at the severity appropriate anatomical level measured by MRI over 12 months between L-serine treated and placebo treated groups

Key secondary outcome(s)
1. Charcot-Marie-Tooth neuropathy score (CMTNS)/ Charcot-Marie-Tooth examination score (CMTES), a validated scale of clinical impairment assessing symptoms, signs and neurophysiological parameters, performed at baseline and 12 months
2. Quality of life questionnaire (CMT health index quality of life) to assess measured at baseline and 12 months
3. Assessment of neuropathic pain using questionnaires: Neuropathic Pain Symptom Inventory (NPSI), Neuropathic pain diagnostic questionnaire (DN4) and Brief pain inventory (BPI) and pain diary at baseline and 12 months

Completion date
30/09/2025

Eligibility

Key inclusion criteria
1. Participants aged ≥18 years with genetically proven HSN1 due to SPTLC1/2 mutations.
2. Participants must be able to undergo an MRI scan without sedation.
3. Participants must be able to complete the Charcot Marie Tooth Examination Score (CMTES)
4. Participants must have a CMTES ≤26
5. Female participants of childbearing potential who are sexually active must agree to use a highly effective method of contraception from the time consent is signed until six days after treatment discontinuation (this is due to a lack of safety data on use of L-serine in pregnant and breastfeeding women; and to allow for medication wash out post treatment discontinuation). Highly effective methods of contraception include:
5.1. Combine hormonal contraception associated with inhibition of ovulation
5.2. Progesterone only hormonal contraception associated with inhibition of ovulation
5.3. Intrauterine device
5.4. Intrauterine hormone-releasing system
5.5. Bilateral tubal occlusion
5.6. Vasectomised partner (when this is the sole partner of the patient)
5.7. Sexual abstinence (sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period associated with the study treatments, and the reliability of sexual abstinence is in line with the usual lifestyle of the subject)
6. Participants must be willing and able to provide written informed consent.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit

18 Years

Upper age limit
100 Years

Sex
All

Total final enrolment
29

Key exclusion criteria
1. Participants have undergone foot surgery in the 6 months prior to trial enrolment or are due to undergo foot surgery during the trial.
2. Participants have a history of nephrolithiasis.
3. Participants have another medical condition or metal implant which precludes them from having an MRI scan
4. Participants have another medical condition which precludes them from completing CMESv2.
5. Participants with known diagnosis of another neuromuscular disease.
6. Participants with type 1 and 2 diabetes.
7. Females who are pregnant or are planning pregnancy or breastfeeding.
8. Patient taking regular L-serine supplementation within 6 months of study commencement.

Date of first enrolment
01/08/2023

Date of final enrolment
30/08/2024

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
National Hospital for Neurology & Neurosurgery
Queen Square
London
England
WC1N 3BG

Sponsor information

Organisation
University College London

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Charity

Funder Name
Charcot-Marie-Tooth Association

Alternative Name(s)
CMT Association, CMTA

Funding Body Type
Government organisation

Funding Body Subtype
Associations and societies (private and public)

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan
All data will be handled in accordance with the UK Data Protection Act 2018. The Sponsor will act as the custodian for the trial data. Each participant will be given a unique trial identification number at the start and used on their records as soon as registered on the study database. Their name and other identifiable information will be kept in a separate database. Data will be held on a purpose-built database and will be password-protected, data from each individual will be listed under their patient identification number (PIN).

The datasets generated during and/or analysed during the current study are/will be available upon request from the SENSE team.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			26/07/2023	No	No

Participant information sheet	version 2.0	28/02/2023	06/03/2023	No	Yes