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A patient study to determine the effectiveness of a needle-free test for the diagnosis of adrenal insufficiency

Submission date
09/03/2024

Recruitment status
Recruiting

Registration date
22/05/2024

Overall study status
Ongoing

Last Edited
10/06/2025

Condition category
Nutritional, Metabolic, Endocrine

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
The adrenal glands produce cortisol, an essential hormone that is released as part of the body's stress response and helps and to control blood pressure and blood sugar levels. Adrenal insufficiency (AI) describes the inability of the body to produce adequate levels of cortisol which, without treatment with replacement cortisol, can lead to serious illness and death. The Short Synacthen Test (SST) is the most popular diagnostic test for AI worldwide. Synacthen (tetracosactide) is a drug which stimulates the adrenal glands to produce cortisol. The SST requires intravenous cannulation and blood sampling before and after the Synacthen is given. It is thus invasive, requires trained staff to deliver the test, and is unpleasant for the patient, especially children. A non-invasive, needle-free alternative to the SST has been developed, the Nasacthin test, with the tetracosactide given nasally via a spray, and the resultant cortisol and cortisone (the salivary equivalent to cortisol) response measured in saliva samples. The STARLIT-3 study will be looking to compare if the Nasacthin test is as good as the SST at diagnosing AI.

Who can participate?
The study will be performed in men, women and children aged 4-75 years living with AI.

What does the study involve?
Study visits will take place across two Clinical Research Facilities (CRFs), the Royal Hallamshire Hospital for adult participants, and Sheffield Children's Hospital for children and young people. Participants will attend two separate study visits, and will receive a different study drug at each visit (either IV Synacthen or Nasacthin). The order in which they receive the drugs will be decided randomly before the first visit. Participants will be asked to provide pairs of samples (one blood and one saliva) at baseline (pre-drug) and then at 30 and 60 minutes after the drug is given. Participants will also be asked to complete a short paper questionnaire during each visit about their experience of having the test, and additional short questionnaire at the final visit to compare the two tests. All participants will receive a safety telephone call 24-48 hours after each study visit to check for any adverse events.

What are the possible benefits and risks of participating?
While there will be no direct benefit to participants, the study will be an important step in the development of the test towards its routine use in the NHS, which would ultimately benefit patients being investigated for AI in the future.

The study participants may include children, who are classed as a vulnerable group. The Sheffield Children's Hospital team have extensive experience in running drug trials involving children, and all study visits for child participants will take place on a specialist children's CRF, with trained staff. Age-appropriate study documents have been developed to help any potential child participants to fully understand what the trial involves, and assent will be obtained from children aged <16 years if appropriate to enable child participants to be involved in the decision-making process.

Participants must have an intravenous cannula inserted at each visit for IV drugs to given and for blood sampling to enable the two tests to be directly compared. This may be briefly painful, or can cause bruising or local swelling after it has been removed.

Synacthen and Nasacthin do not cause any long-term side effects, but mild and short-lived effects such as watery eyes, sneezing, coughing or a vinegary taste may be experienced after the nasal spray, and with both drugs there is also a very small risk of a potentially severe allergic reaction. Any patients with a past history of severe allergic reactions or anaphylaxis will be excluded from the study.

Where is the study run from?
The University of Sheffield (UK)

When is the study starting and how long is it expected to run for?
March 2024 to November 2025

Who is funding the study?
Medical Research Council (MRC) (UK)

Who is the main contact?
Dr Charlotte Elder, c.j.elder@sheffield.ac.uk

Study website
https://hhtu.hull.ac.uk/starlit-3

Contact information

Type(s)
Public

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Type(s)
Scientific, Principal Investigator

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1009462

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
SCH-2732c, IRAS 1009462, CPMS 61674

Study information

Scientific Title
Clinical Validation of a Non-Invasive Diagnostic Test for Adrenal Insufficiency using Comparative Pharmacodynamic Equivalence in a Patient Population Salivary Test of Adrenal Response to Liquid Intranasal Tetracosactide - Study 3 (STARLIT-3)

Acronym
STARLIT-3

Study objectives

Current study hypothesis as of 10/06/2025:
Primary objective:
To show that adrenal function testing with 500 micrograms Nasacthin is able to correctly diagnose patients with AI by estimating the proportion of patients with AI diagnosed by the Nasacthin Test out of those known to have AI (as detected by the SST) (Positive Percent Agreement) using serum cortisol at 30 minutes.

Secondary objectives:
1. To show that adrenal function testing with 500 micrograms Nasacthin is able to correctly diagnose patients with AI by estimating the proportion of patients with AI diagnosed by the Nasacthin Test out of those known to have AI (as detected by the SST) (Positive Percent Agreement) using serum cortisol at 60 minutes.
2. To demonstrate the safety of Nasacthin using AEs, SAEs and SUSARs.
3. To explore the acceptability, usability and tolerability of Nasacthin administration in healthcare professionals and participants.

Previous study hypothesis:
Primary objective:
To show that adrenal function testing with 500 micrograms Nasacthin is able to correctly diagnose patients with AI by estimating the proportion of patients with AI diagnosed by the Nasacthin Test out of those known to have AI (as detected by the SST) (Positive Percent Agreement) using serum cortisol at 30 minutes.

Secondary objectives:
1. To demonstrate the safety of Nasacthin using AEs, SAEs and SUSARs.
2. To explore the acceptability, usability and tolerability of Nasacthin administration in healthcare professionals and participants.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 20/05/2024, South Central - Hampshire A Research Ethics Committee (Health Research Authority, 2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; 0207 104 8210; hampshirea.rec@hra.nhs.uk), ref: 24/SC/0102

Study design
Interventional open randomized cross over controlled trial

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Hospital

Study type(s)
Safety, Efficacy

Participant information sheet
https://hhtu.hull.ac.uk/starlit-3/#tab-10804

Health condition(s) or problem(s) studied
Adrenal insufficiency

Interventions
Participants will attend 2 separate visits and will receive a different drug (either 500µg nasal tetracosactide (Nasacthin) or 250µg IV tetracosactide (Synacthen) (or 145µg/m2 for paediatric participants)) at each visit in an open-label, randomised sequence, determined in advance of the first visit via an integrated randomisation function within the study's secure web-based data capture system. For each drug, there is a single administration on the day of the visit.

The nasal formulation (Nasacthin) is administered using a primed mucosal atomiser device, 0.1ml to each nostril (total volume 0.2ml). Synacthen is administered via the cannula as a slow bolus.

All participants will be asked to complete a short questionnaire during each visit to explore the acceptability and tolerability of the study drug and will also receive a safety telephone call from a member of the study team 24-48 hours after each visit to check for any adverse events. Participants will also have the option to take part in a focus group held at the end of the study to explore the acceptability, usability and tolerability of the Nasacthin test.

Intervention Type
Drug

Pharmaceutical study type(s)
Diagnosis

Phase
Phase III

Drug/device/biological/vaccine name(s)
Nasacthin, Synacthen [Tetracosactide]

Primary outcome measure
The proportion of participants with adrenal insufficiency (AI) diagnosed by the Nasacthin Test (Positive Percent Agreement) using serum cortisol at baseline and 30 minutes post-drug administration, measured using liquid chromatography with tandem mass spectrometry (LC-MS /MS). To be included in the analysis, participants will have been confirmed to have AI by assessment of serum cortisol at 30 minutes following the Synacthen test.

Secondary outcome measures
Current secondary outcome measures as of 03/03/2025:

1. The proportion of participants with adrenal insufficiency (AI) diagnosed by the Nasacthin Test (Positive Percent Agreement) using serum cortisol at baseline and 60 minutes post-drug administration, measured using liquid chromatography with tandem mass spectrometry (LC-MS /MS). To be included in the analysis, participants will have been confirmed to have AI by assessment of serum cortisol at 30 minutes following the Synacthen test.
2. Frequency of adverse events (AEs), serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs) by treatment arm, as reported by participants up to 48 hours

after each study visit. Any SAEs/SUSARs will be followed to the point of resolution.
3. Analysis of participant and healthcare professional acceptability, usability and tolerability of the Nasacthin test, measured using non-validated questionnaires completed by participants at the end of each study visit and by healthcare professionals at the end of the study; and optional participant and stakeholder focus groups held at the end of the study.

Previous secondary outcome measures:

1. Frequency of adverse events (AEs), serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs) by treatment arm, as reported by participants up to 48 hours after each study visit. Any SAEs/SUSARs will be followed to the point of resolution.
2. Analysis of participant and healthcare professional acceptability, usability and tolerability of the Nasacthin test, measured using non-validated questionnaires completed by participants at the end of each study visit and by healthcare professionals at the end of the study; and optional participant and stakeholder focus groups held at the end of the study.

Overall study start date
07/03/2024

Completion date
30/11/2025

Eligibility

Key inclusion criteria
Current inclusion criteria as of 03/03/2025:

1. Known adrenal insufficiency
2. Confirmation of adrenal insufficiency with either a waking salivary cortisone of <7 nmol/L, basal cortisol <100 nmol/L or peak on SST <200 nmol/L at time of diagnosis or since
3. Able to comply with passive drool salivary sampling requirements
4. Able to provide signed written informed consent
5. Age 4-75 years

Previous inclusion criteria:

1. Known adrenal insufficiency
2. Basal cortisol <100 nmol/L or peak on SST <200 nmol/L at time of diagnosis or since in last 6 months
3. Able to comply with passive drool salivary sampling requirements
4. Able to provide signed written informed consent
5. Age 4-75 years

Participant type(s)
Patient

Age group

Mixed

Lower age limit
4 Years

Upper age limit
75 Years

Sex
Both

Target number of participants
41

Key exclusion criteria
Current exclusion criteria as of 03/03/2025:

1. Ongoing pregnancy
2. Use of oestrogen-containing hormonal contraception / Hormone Replacement Therapy (due to the effect on cortisol levels)
3. Co-morbid condition requiring daily administration of a medication that interferes with the metabolism of glucocorticoids, e.g. known to affect corticosteroid-binding globulin (CBG), including all oestrogens, or the hypothalamic-pituitary-adrenal (HPA) axis, such as loperamide, oral antifungals and opiates
4. Currently prescribed anti-epileptic medication, such as sodium valproate, phenytoin, clonazepam, nitrazepam, phenobarbital or primidone
5. Currently prescribed amphetamines, e.g. lisdexamfetamine, dexamphetamine
6. Known and active protein losing disorder, e.g. enteropathy or nephrotic syndrome, which may result in a cortisol binding globulin abnormality
7. Known clinical or biochemical evidence of hepatic or renal disease. Creatinine over twice the upper limit of normal (ULN) or elevated liver function tests (alanine transaminase (ALT) or aspartate transaminase (AST) >3 times the ULN
8. Current uncontrolled active infection (may include later in the trial at clinician's discretion if completely resolved)
9. Known or suspected alcohol dependence or drug misuse
10. Current smoker or vaper (or within 6 months of cessation)
11. Recent (within last 1 week) liquorice ingestion (preparations containing glycyrrhizic acid only)
12. History of known salivary gland or oral mucosa pathology or unable to produce a suitable salivary sample (e.g. as a consequence of drugs that cause dry mouth)
13. Previous severe allergic reaction or anaphylaxis, or adverse reaction to any antigen of ACTH or Synacthen
14. Participation in another clinical trial of an investigational or licensed drug or device within the last 3 months
15. Unable to comply with the requirements of the protocol
16. Any other significant medical or psychiatric conditions that in the opinion of the investigator would preclude participation in the trial
17. For nasal visit only - active nasal symptoms, including Coryzal symptoms within the last week, active allergic rhinitis (hayfever) symptoms currently requiring medication, or heavy nosebleed within the previous 48 hours - just excluded from that visit

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Previous exclusion criteria:

1. Ongoing pregnancy
2. Use of oestrogen-containing hormonal contraception / Hormone Replacement Therapy (due to the effect on cortisol levels)
3. Co-morbid condition requiring daily administration of a medication that interferes with the metabolism of glucocorticoids, e.g. known to affect corticosteroid-binding globulin (CBG), including all oestrogens, or the hypothalamic-pituitary-adrenal (HPA) axis, such as loperamide, oral antifungals and opiates
4. Known and active protein losing disorder, e.g. enteropathy or nephrotic syndrome, which may result in a cortisol binding globulin abnormality
5. Known clinical or biochemical evidence of hepatic or renal disease. Creatinine over twice the upper limit of normal (ULN) or elevated liver function tests (alanine transaminase (ALT) or aspartate transaminase (AST) >3 times the ULN
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11. Previous severe allergic reaction or anaphylaxis, or adverse reaction to any antigen of ACTH or Synacthen
12. Participation in another clinical trial of an investigational or licensed drug or device within the last 3 months
13. Unable to comply with the requirements of the protocol
14. Any other significant medical or psychiatric conditions that in the opinion of the investigator would preclude participation in the trial
15. For nasal visit only - Coryzal symptoms within the last week - just excluded from that visit

Date of first enrolment
01/02/2025

Date of final enrolment
31/08/2025

Locations

Countries of recruitment
United Kingdom

Study participating centre
Sheffield Childrens Hospital
Western Bank
Sheffield
United Kingdom
S10 2TH

Study participating centre
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United Kingdom
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Sponsor information

Organisation
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Sponsor type
Hospital/treatment centre

Website
https://www.sheffieldchildrens.nhs.uk/

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Peer reviewed scientific journals
Internal report
Conference presentation
Publication on website
Other publication
Submission to regulatory authorities
The anonymised data generated by the study will be suitable for sharing, e.g. for further research analysis and meta-analysis. Final anonymised clinical study datasets and meta-data will be produced by the HHTU data team and stored in an appropriate format to enable discoverability and sharing within the national data repository available to Medical Research Council researchers, ReSHARE. The University of Sheffield data repository ORDA will be utilised to enhance the discoverability of the data with meta-data being publicly available.

Intention to publish date
30/06/2026

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request.

IPD sharing plan summary
Available on request