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

Submission date
17/02/2023

Recruitment status
No longer recruiting

Registration date
28/09/2023

Overall study status
Completed

Last Edited
20/01/2026

Condition category
Nutritional, Metabolic, Endocrine

[X] Prospectively registered
[X] 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 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-2 study will be looking to verify that the Nasacthin test does not produce a lower cortisol response compared to the SST.

Who can participate?
Healthy men, women and children aged 4-69 years old

What does the study involve?
Participants will attend 4 separate study visits and will receive a different drug at each visit (either nasal tetracosactide (Nasacthin), nasal placebo, IV tetracosactide (Synacthen) or IV placebo). The order in which they receive the drugs will be decided randomly before their first visit. Participants will be asked to provide pairs of samples (one blood and one saliva sample) at baseline (pre-drug) and then at 30, 60, 90 and 120 minutes after the drug is given. Additional saliva samples will be collected by participants at home after 180, 240, 360 and 480 minutes, and returned to the study team. All participants will receive a safety telephone call 24-48 hours after each study visit to check for any adverse events.

Participants will also be asked to complete a short paper questionnaire at each of the visits during the 90- and 120-minute sample interval, to explore the acceptability and tolerability of

the study drug they received at that visit, and of the associated study procedures. During the final visit, participants will be asked to complete an additional short questionnaire, which will ask about the overall acceptability and tolerability, comparing both the nasal and IV tests.

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.

Participants must have a cannula inserted at each visit for IV drugs to be given and for blood sampling, which may be briefly painful or can rarely cause slight bruising or local swelling. 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.

There is also a very small chance that the sample results might show lower-than-normal levels of cortisol in response to the drugs, which would require further investigation via the standard care pathway.

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

When is the study starting and how long is it expected to run for?
September 2022 to June 2026

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

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

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Additional identifiers

Integrated Research Application System (IRAS)
1006488

Central Portfolio Management System (CPMS)
55547

Protocol serial number
SCH-2732b

Study information

Scientific Title
Clinical validation of a non-invasive diagnostic test for adrenal insufficiency using comparative pharmacodynamic equivalence in a healthy population

Acronym
STARLIT-2

Study objectives
Current study hypothesis as of 09/10/2024:
A. To determine whether 500mcg Nasacthin and 250mcg Synacthen produce a similar rise in serum cortisol levels at 30 minutes (using the values measured in the analysis).
B. To determine the proportion of participants for which the Nasacthin produced a rise above a certain value at 30 minutes, out of the total participants for which Synacthen produced a rise above the same value.
C. To determine whether the Nasacthin active treatment induces a response in serum cortisol levels at 30 minutes compared to the placebo treatment (using change from levels measured at baseline).
D. To determine whether the Synacthen active treatment induces a response in serum cortisol

levels at 30 minutes compared to the placebo treatment (using change from levels measured at baseline).
E. To determine whether 500mcg Nasacthin and 250mcg Synacthen produce a similar rise in salivary cortisone levels at 60 minutes (using the values measured in the analysis).
F. To determine whether 500mcg Nasacthin and 250mcg Synacthen produce a similar rise in serum cortisol levels at 30 minutes (using change from levels measured at baseline).
G. To determine whether 500mcg Nasacthin and 250mcg Synacthen produce a similar rise in serum cortisol levels at 60 minutes (using the values measured in the analysis).
H. To determine whether 500mcg Nasacthin and 250mcg Synacthen produce a similar rise in serum cortisol levels at 60 minutes (using change from levels measured at baseline).
I. To demonstrate the safety of Nasacthin by recording any adverse events occurring during the study.
J. To explore the acceptability, usability and tolerability of Nasacthin administration in staff and participants.

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A. To determine whether 500mcg Nasacthin and 250mcg Synacthen produce a similar rise in serum cortisol levels at 30 minutes (using the values measured in the analysis).
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C. To determine whether the Nasacthin active treatment induces a response in serum cortisol levels at 30 minutes compared to the placebo treatment (using change from levels measured at baseline).
D. To determine whether the Synacthen active treatment induces a response in serum cortisol levels at 30 minutes compared to the placebo treatment (using change from levels measured at baseline).
E. To determine whether 500mcg Nasacthin and 250mcg Synacthen produce a similar rise in salivary cortisone levels at 60 minutes (using the values measured in the analysis).
F. To determine whether 500mcg Nasacthin and 250mcg Synacthen produce a similar rise in serum cortisol levels at 30 minutes (using change from levels measured at baseline).
G. To demonstrate the safety of Nasacthin by recording any adverse events occurring during the study.
H. To explore the acceptability, usability and tolerability of Nasacthin administration in staff and participants.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 21/09/2023, South Central – Hampshire A Research Ethics Committee (Health Research Authority, 2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)20 710 48120; hampshirea.rec@hra.nhs.uk), ref: 23/SC/0073

Primary study design
Interventional

Study design
Randomized placebo-controlled double-blinded four-way cross-over study

Study type(s)

Diagnostic, Efficacy, Safety

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

Interventions
Participants will attend 4 separate visits and will receive a different drug (either 500µg nasal tetracosactide (Nasacthin), nasal placebo, 250µg IV tetracosactide (Synacthen) (or 145µg/m2 for paediatric participants) or IV placebo) at each visit in a double-blind, 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.

Nasal formulations (Nasacthin/nasal placebo) are administered using a primed mucosal atomiser device, 0.1ml to each nostril (total volume 0.2ml). Synacthen and IV placebo are 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.

In addition, at the end of the study, healthcare professionals involved in delivering the study will be asked to complete a questionnaire on the comparative acceptability of administration of the tests, and a focus group of key stakeholders (e.g. endocrinologists, nurses, clinicians from other heavy steroid-using specialities, primary and community care providers, commissioners and service managers) will be convened to discuss the usability and practicalities of the different testing methods.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Nasal tetracosactide (Nasacthin), intravenous tetracosactide (Synacthen)

Primary outcome(s)
1. Comparison of mean serum cortisol concentration post-Nasacthin and Synacthen administration, measured using liquid chromatography with tandem mass spectrometry (LC-MS /MS) at baseline (pre-drug) and 30 minutes post-drug administration
2. Proportion of participants for which the Nasacthin test produces a rise above a pre-set threshold, out of those for whom the Synacthen test also produces a rise above a pre-set threshold, measured using LC-MS/MS at baseline and 30 minutes post-drug administration
3. Comparison of mean change from baseline in serum cortisol concentration post-active Nasacthin and nasal placebo administration, measured using LC-MS/MS at baseline and 30 minutes post-drug administration
4. Comparison of mean change from baseline in serum cortisol concentration post-active Synacthen and IV placebo administration, measured using LC-MS/MS at baseline and 30 minutes post-drug administration

Key secondary outcome(s)
Current secondary outcome measures as of 09/10/2024:
1. Comparison of mean salivary cortisone concentration post-Nasacthin and Synacthen administration, measured using LC-MS/MS at baseline and 60 minutes post-drug administration.
2. Comparison of mean change from baseline in serum cortisol concentration post-Nasacthin and Synacthen administration, measured using LC-MS/MS at baseline and 30 minutes post-drug administration.
3. Comparison of mean serum cortisol concentration post-Nasacthin and Synacthen administration, measured using liquid chromatography with tandem mass spectrometry (LC-MS /MS) at baseline (pre-drug) and 60 minutes post-drug administration.
4. Comparison of mean change from baseline in serum cortisol concentration post-Nasacthin and Synacthen administration, measured using LC-MS/MS at baseline and 60 minutes post-drug administration.
5. Frequency of adverse events (AEs), serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs) by the treatment arm, as reported by participants up to 48 hours after the study visit.
6. Analysis of participant and clinical workforce acceptability, usability and tolerability, measured using non-validated questionnaires, for participants at each study visit and for healthcare professionals at the end of the study; optional participant interviews after completion of study visits; and a stakeholder focus group at the end of the study.

Previous secondary outcome measures:
1. Comparison of mean salivary cortisone concentration post-Nasacthin and Synacthen administration, measured using LC-MS/MS at baseline and 60 minutes post-drug administration.
2. Comparison of mean change from baseline in serum cortisol concentration post-Nasacthin and Synacthen administration, measured using LC-MS/MS at baseline and 30 minutes post-drug administration.
3. Frequency of adverse events (AEs), serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs) by the treatment arm, as reported by participants up to 48 hours after the study visit.
4. Analysis of participant and clinical workforce acceptability, usability and tolerability, measured using non-validated questionnaires, for participants at each study visit and for healthcare professionals at the end of the study; optional participant interviews after completion of study visits; and a stakeholder focus group at the end of the study.

Completion date
30/06/2026

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 17/11/2023:
1. Healthy men, women and children aged 4-69 years old
2. Able to comply with passive drool salivary sampling requirements
3. Provision of signed written informed consent

Previous participant inclusion criteria:
1. Healthy men, women and children aged 2-69 years old
2. Able to comply with passive drool salivary sampling requirements
3. Provision of signed written informed consent

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
4 Years

Upper age limit
69 Years

Sex
All

Total final enrolment
38

Key exclusion criteria
Current participant exclusion criteria as of 09/10/2024:
1. Known adrenal insufficiency, Cushing's syndrome or any other adrenal or pituitary gland disorder
2. Ongoing pregnancy
3. Use of oestrogen-containing hormonal contraception / Hormone Replacement Therapy (due to the effect on cortisol levels)
4. Known 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, including opioids, oral antifungals, loperamide
5. Currently prescribed anti-epileptic medication, such as sodium valproate, phenytoin, clonazepam, nitrazepam, phenobarbital or primidone
6. Known and active protein-losing disorders, e.g. enteropathy or nephrotic syndrome, who may have 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. Participants on regular, inhaled, topical, nasal, ocular, rectal, oral or intra-articular steroids for any indication in the last 3 months
9. Current uncontrolled active infection
10. BMI >35 kg/m² (or BMI >3 standard deviations (SD) above the mean for age and sex if <16 years)
11. Known or suspected alcohol dependence or drug misuse
12. Current smoker or vaper (or within 6 months of cessation)
13. Recent (within 1 week) liquorice ingestion (preparations containing glycyrrhizic acid only)
14. Individuals with a history of known salivary gland or oral mucosa pathology who are unable to produce a suitable salivary sample (e.g. as a consequence of drugs that cause dry mouth)
15. Previous severe allergic reaction or anaphylaxis or adverse reaction to any antigen of ACTH or Synacthen

16. Participation in another clinical trial of an investigational or licensed drug within the 3 months prior to inclusion in study, unless it is a clinical trial of the same IMP (i.e. Nasacthin), in which case only a 7-day washout period applies
17. Participants unable to comply with the requirements of the protocol
18. Participants with any other significant medical or psychiatric conditions that in the opinion of the investigator would preclude participation in the trial
19. For nasal visits only: coryzal symptoms within the last week (and will be asked to report any new symptoms occurring within 24 hours of the test) or heavy nosebleed within the previous 48 hours - just excluded from that visit

Previous participant exclusion criteria:
1. Known adrenal insufficiency, Cushing's syndrome or any other adrenal or pituitary gland disorder
2. Ongoing pregnancy
3. Use of oestrogen-containing hormonal contraception / Hormone Replacement Therapy (due to the effect on cortisol levels)
4. Known 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, including opioids, oral antifungals, loperamide
5. Known and active protein-losing disorders, e.g. enteropathy or nephrotic syndrome, who may have a cortisol-binding globulin abnormality
6. 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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17. Participants with any other significant medical or psychiatric conditions that in the opinion of the investigator would preclude participation in the trial
18. For nasal visits only: coryzal symptoms within the last week (and will be asked to report any new symptoms occurring within 24 hours of the test)

Date of first enrolment
14/12/2023

Date of final enrolment
20/04/2025

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Sheffield Childrens Hospital
Western Bank
Sheffield
England
S10 2TH

Study participating centre
Royal Hallamshire Hospital
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Sponsor information

Organisation
Sheffield Children's NHS Foundation Trust

ROR
https://ror.org/02md8hv62

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

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

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		22/12/2024	20/01/2025	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes