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Blocking cortisol metabolism to improve mild Cushing's syndrome due to an adrenal nodule

Submission date
09/02/2024

Recruitment status
Recruiting

Registration date
27/03/2024

Overall study status
Ongoing

Last Edited
09/04/2024

Condition category
Nutritional, Metabolic, Endocrine

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

Plain English summary of protocol

Background and study aims
Benign nodules of the adrenal gland are common and can frequently produce too much of the steroid stress hormone cortisol (a condition called mild autonomous cortisol secretion [MACS]). It is estimated that 3% of the population over 70 have MACS and this is associated with increased risks of frailty, development of diabetes, heart attacks and strokes. Cortisol has profound effects on many tissues including the circulatory system, fat, muscle and the brain. Currently, there is no specific treatment to limit the effects in patients with MACS.
In tissues (fat, muscle, liver, bone, brain) researchers have shown that there is further generation of excess cortisol through the activity of an enzyme called 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1); this exacerbates the problem of too much cortisol and drives many of the adverse features that we observe in patients with MACS. Using a drug to block the action of this enzyme, a so-called 11β-HSD1 inhibitor, the researchers have been able to block the undesirable effects of prescribed steroids that have been taken by mouth. They now want to see if using a similar approach in patients with MACS improves their symptoms by reducing the action of the naturally occurring cortisol that is present at slightly higher levels in their bodies. They will use very sensitive techniques to look at how the body handles glucose, as well as fat and muscle distribution, brain function and bone health, which are all well-documented to be adversely affected in patients with MACS. The aim is to discover if these are improved with an 11β-HSD1 inhibitor (SPI-62). These studies will not only demonstrate the fundamental role of 11β-HSD1 in the development of MACS, but also begin to explore the potential that 11β-HSD1 inhibitors may be an option for future drug treatment in these patients where currently none are available.

Who can participate?
Patients aged 18 years and over with MACS

What does the study involve?
Participants undergo 2 days of baseline investigations. They will then be randomly allocated to take SPI-62 or a placebo (dummy drug) for 12 weeks. Follow-up visits will occur 4, 8 and 12 weeks after treatment is started. All baseline investigations are repeated after 12 weeks of SPI-62 or placebo treatment.

What are the possible benefits and risks of participating?
SPI-62 has been administered to 165 subjects in four completed clinical trials, as single doses of up to 60 mg and multiple QD doses of up to 50 mg for 2 weeks in healthy young and elderly adult subjects, and multiple QD doses of 10 mg for 6 weeks in subjects with painful diabetic peripheral neuropathy (PDPN).
There have been no deaths. The only serious adverse event (SAE) considered related to SPI-62 was thrombocytopenia in a subject with an undisclosed history of idiopathic thrombocytopenic purpura (this is now an exclusion criterion for the current study). An SAE, not related to SPI-62, of post-surgical pain resulted in the only other safety-related discontinuation. There were no other SAEs or AEs that led to discontinuation.
Most AEs reported by SPI-62 subjects were mild in severity. Across all trials, headache was reported by 9.7% of SPI-62 subjects compared to 4.4% of placebo subjects. No other trends in AEs were noted.
One subject with PDPN with a high baseline alanine aminotransferase measurement increased to > 3 times the upper limit of normal which resolved within two weeks during continued treatment, with no elevation of aspartate aminotransferase or bilirubin. Sporadic potentially clinically significant changes in orthostatic vital signs and possibly related AEs (e.g., dizziness) were observed mainly following SPI-62 20 to 50-mg doses. No other potential safety signals from clinical laboratory measurements or vital signs were noted.
There were no clinically significant trends in individual electrocardiogram (ECG) results. An analysis of SPI-62 concentrations and QT interval corrected (QTC) for heart rate using Fridericia's method concluded that SPI-62 had no clinically significant effect on prolonging cardiac repolarization following QD doses up to 50 mg.
Venepuncture and cannulae insertion may cause discomfort and bruising. There is a possible risk for clotting or infection, but these are minimized by the use of good clinical practice and sterile techniques.
There is the potential risk of low blood sugar at the end of the clamp procedure, but all volunteers are provided with a meal and their blood sugar levels are measured repeatedly to ensure that they are stable.
The total amount of blood taken during any individual study day (visits 3 and 7) will be a maximum of 220 ml, about two-thirds of what might be given at a normal blood donation.
During the research visits, the researchers will ensure participants stay well hydrated and before leaving the CRU at the end of the study they will have a light meal.
The stable isotopes (glucose) will be obtained from CK Gas Ltd. and have been tested for human use.
The dual-energy x-ray absorptiometry scans will involve exposure to a small radiation dose, but much lower than a standard chest X-ray (<2 days background radiation). The single-slice CT scan and the DXA scan together due to their radiation exposure do have a very small associated increased cancer risk. We are all at risk of developing cancer during our lifetime. The normal risk is that this will happen to about 50% of people at some point in their life. Taking part in this study will increase the chances of this happening to you from 50% to 50.18%. The lowest doses of radiation exposure to successfully acquire the scans are used to minimise risk.
There is a small risk of infection and bruising after inserting microdialysis catheters or taking the fat biopsy. This is minimised using sterile techniques and applying appropriate pressure.

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

When is the study starting and how long is it expected to run for?
February 2024 to December 2026

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

Who is the main contact?
Dr Jeremy Tomlinson, jeremy.tomlinson@ocdem.ox.ac.uk

Contact information

Type(s)
Scientific, Principal Investigator

Contact name
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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1004412

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
IRAS 1004412

Study information

Scientific Title
Dissecting the Contribution of glucocorticoid metabolism in Mild Autonomous Cortisol Secretion: a randomised controlled trial of the 11β-HSD1 inhibitor SPI-62

Acronym
DC-MACS

Study objectives

Primary objective:
To determine the ability of SPI-62 compared to placebo to improve glucose use in patients with mild autonomous cortisol secretion (MACS).

Secondary objectives:
1. To determine the ability of SPI-62 compared to placebo to improve circulating markers of bone turnover
2. To determine the ability of SPI-62 compared to placebo to improve cognitive, neurological and behavioural function
3. To determine the ability of SPI-62 compared to placebo to improve blood pressure
4. To determine the ability of SPI-62 compared to placebo to improve hepatic insulin sensitivity
5. To determine the ability of SPI-62 compared to placebo to improve body composition (fat distribution, lean and fat mass)
6. To determine the ability of SPI-62 compared to placebo to improve circulating inflammatory cytokines and inflammatory responses in circulating inflammatory cells
7. To determine the ability of SPI-62 compared to placebo to improve glucose levels.
8. To determine the ability of SPI-62 compared to placebo to alter adipose tissue gene expression profile
9. To determine the safety and tolerability of SPI-62 compared to placebo

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 25/03/2024, London - Central Research Ethics Committee (3rd Floor, 3 Piccadilly Place, London Road, Manchester, M1 3BN, United Kingdom; +44 207 104 8225; londoncentral.rec@hra.nhs.uk), ref: 24/LO/0171

Study design
Randomized double-blind placebo-controlled parallel-group trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Safety, Efficacy

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Mild autonomous cortisol secretion due to an adrenal adenoma

Interventions

40 patients with Mild Autonomous Cortisol Secretion (MACS) will be recruited and undergo 2 days of baseline investigations. They will then be randomized using an online tool to receive the IMP (SPI-62 6 mg once daily, n = 20) or placebo (n = 20) for 12 weeks. Follow-up visits will occur 4, 8 and 12 weeks after treatment is started. All baseline investigations are repeated after 12 weeks of SPI-62 or placebo treatment.

Intervention Type
Drug

Pharmaceutical study type(s)
Not Applicable

Phase
Phase II

Drug/device/biological/vaccine name(s)
SPI-62

Primary outcome measure
Glucose disposal as measured across the hyperinsulinaemic euglycaemic clamp using stable isotope glucose tracers at baseline and 12 weeks

Secondary outcome measures
1. Serum markers of bone turnover including Procollagen type 1 N-terminal pro-peptide, type I collagen cross-linked N-telopeptide and osteocalcin measured using ELISAs at 4, 8 and 11 weeks
2. Cognitive function assessed using the CogState battery of tests at baseline and 11 weeks
3. 24-hour ambulatory blood pressure measurements using an ambulatory blood pressure monitor at baseline and 11 weeks
4. Endogenous glucose production rate during a hyperinsulinaemic euglycaemic clamp measured using stable isotope glucose tracers at baseline and 11 weeks
5. Total and regional lean and fat mass on DXA scan and intra-abdominal fat mass on single slice CT image at baseline and 11 weeks
6. Steroid metabolites measured by gas chromatography, mass spectrometry in a timed overnight urine sample at 4, 8 and 11 weeks
7. Circulating inflammatory cytokines, isolation of peripheral blood mononuclear cells and defining their response to inflammatory stress measured using cell proliferation assays and ELISAs at baseline and 11 weeks
8. Continuous glucose monitoring using interstitial glucose sensors at baseline, 4-6 and 8-10 weeks
9. Gene expression changes measured in adipose tissue biopsies using PCR gene expression analysis at baseline and 11 weeks
10. Safety and tolerability measured using clinical data and serum biochemical assessments at baseline and 11 weeks

Overall study start date
07/02/2024

Completion date
31/12/2026

Eligibility

Key inclusion criteria
1. Participant is willing and able to give informed consent for participation in the trial
2. Aged 18 years or above
3. 09.00 h serum cortisol >51 nmol/L after overnight dexamethasone (1 mg) within the last 6 months performed in the absence (for at least 4 weeks prior to testing) of concomitant estrogen-containing medication.
4. Adrenal adenoma(s) that has (have) not been surgically removed, and with benign characteristics on cross-sectional imaging.
5. Body mass index 18 to 45 kg/m2
6. Stable dose of current regular antihypertensive and/or glucose-lowering medication for at least 12 weeks prior to trial entry.
7. Female participants of childbearing potential and male participants whose partner is of childbearing potential must be willing to ensure that they and their partner use effective contraception during the trial and for 90 days thereafter.
8. In the Investigator's opinion, the participant is able and willing to comply with all trial requirements.
9. Participant is willing to allow his or her General Practitioner and consultant, if appropriate, to be notified of participation in the trial

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
40

Key exclusion criteria
1. Female participant is pregnant, lactating, or planning pregnancy during the course of the trial
2. Scheduled elective surgery or other procedures requiring general anaesthesia are required during the course of the trial
3. Participants with a life expectancy of less than 6 months
4. A diagnosis of idiopathic thrombocytopenic purpura or any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial
5. A clinical phenotype consistent with classical Cushing's syndrome (e.g. thin skin, easy bruising, proximal myopathy)
6. Evidence from medical records of elevated aldosterone/renin ratio (above local reference range) on blood sampling
7. Renal impairment indicated by eGFR <60 ml/min/1.73 m^2, calculated using an appropriate and

validated equation
8. Participants with a diagnosis of liver cirrhosis or liver function test (LFT) elevations that exceed 1.5 x the upper limit of normal at screening and require further clinical investigation: LFT pattern consistent with Gilbert's syndrome is allowed
9. Recent (< 1 year) myocardial infarction or stroke, orthostatic or vasovagal syncope
10. QT interval corrected (QTc) interval >500 ms, uncorrected QT interval >600 ms, or evidence of significant, life-threatening arrhythmia or bradycardia (heart rate <45 bpm) according to electrocardiogram (ECG)
11. Anaemia, defined as haemoglobin ≤110 g/L (female) and ≤130 g/L (male)
12. Untreated hypothyroidism
13. Taking a prohibited medication or exposure to a prohibited medication (section 10.6)
14. Current evidence or significant past history of alcohol misuse disorder (> 35 units per week female and >50 units per week male, or other indicators of possible alcohol misuse) in the opinion of the Investigator
15. Uncontrolled hypertension (>160/100 mmHg)
16. Type 1 diabetes or Type 2 diabetes requiring medication (with the exception of metformin monotherapy)
17. Recent (within the last 3 months) or planned night-shift work during the duration of the study
18. Contraindication to any of the study treatments or known or suspected hypersensitivity to the investigational product, compounds of the same class, other study treatments or any excipients
19. Participation in an interventional study in which involvement was completed less than 12 weeks before recruitment into the current study
20. Administration of any vaccine within 4 weeks prior to randomization or planned during the trial
21. SARS-CoV-2 infection within 4 weeks, or hospitalization for COVID-19 disease within 6 months, prior to randomization
22. Any major surgery within 1 month prior to randomization or planned during the trial

Date of first enrolment
04/03/2024

Date of final enrolment
01/07/2026

Locations

Countries of recruitment
United Kingdom

Study participating centre
-
United Kingdom
-

Sponsor information

Organisation
University of Oxford

Sponsor details
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Sponsor type
University/education

Website
http://www.ox.ac.uk/

ROR
https://ror.org/052gg0110

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
1. Peer-reviewed scientific journals
2. Conference presentation
3. Publication on website
4. Submission to regulatory authorities

Intention to publish date
31/12/2027

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date