ISRCTN16167828 https://doi.org/10.1186/ISRCTN16167828

Does adding progesterone to dexamethasone in patients with brain swelling caused by cancer allow the use of lower doses of dexamethasone in the future?

Submission date
21/02/2022

Recruitment status
Stopped

Registration date
24/02/2022

Overall study status
Stopped

Last Edited
20/08/2024

Condition category
Cancer

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

Plain English summary of protocol

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-of-progesterone-for-cancer-spread-to-the-brain-prossper

Background and study aims
Corticosteroids, and in particular dexamethasone, remain central to the management of patients with brain tumours, despite their frequent and often serious side effects. Furthermore, there is increasing evidence that patients who remain on corticosteroids fare worse than those in whom steroids can be withdrawn and not simply because they have worse disease; possible explanations include a radio-protective effect and impaired immune response. The need for an alternative to corticosteroids has become increasingly recognised, but to date no such alternative has been identified. Progesterone is also a steroid, with neuroprotective and anti-inflammatory properties in pre-clinical models, but fewer side effects in patients. Progesterone warrants investigation as an alternative to corticosteroids for patients with brain tumour induced oedema. Unfortunately, pre-clinical models of brain tumours do not replicate the oedema (build-up of fluid) seen in patients, so laboratory studies are of limited value. In addition, the dose of progesterone to achieve optimal drug exposure is unclear. This trial in patients with brain tumours and oedema will investigate the pharmacokinetics (what the body does to the drug) of differing doses of oral progesterone. The researchers also hope to obtain preliminary evidence as to whether the addition of progesterone allows a greater reduction in the dose of dexamethasone for these patients. If successful, this trial will underpin a definitive trial studying the effectiveness of progesterone in patients with primary and metastatic brain tumours with oedema.

Who can participate?
Patients aged 18 years and over with secondary brain cancers with oedema

What does the study involve?
Stage 1: Participants will receive a single oral dose of 200 mg micronised progesterone on Day 1

and a second single 600 mg dose 5 -21 days later. Blood samples will be collected to measure drug levels after each dose of progesterone. Participants will also receive dexamethasone dose on Day 1 but this will be reduced as clinically indicated on other days.
Stage 2: Participants will receive oral micronised progesterone or placebo three times a day and a dose of dexamethasone. The progesterone or placebo will only be taken daily for 14 days. The daily dexamethasone dose will be the same on both sampling days, but can be adjusted as clinically indicated between the sampling days. The treating clinician will advise the dose to take each day. Blood samples will be collected to measure drug and hormone levels; participants will also be asked to complete questionnaires and an interview.

What are the possible benefits and risks of participating?
Benefits: Hopefully this study drug will help reduce the swelling in the brain caused by the brain tumour and will have few, or minor, side effects. It is also hoped that this may be a better treatment than the current medication that is routinely given to patients. It is hoped that this research will teach us more about this type of cancer and how it can be treated. This may enable us to improve the standard of treatment to help other patients with cancer in the future.
Risks:
Stage 1: Participants may be required to attend the clinic more often than people who are not in the study. This is because the research staff may want to see them more often to check on progress.
On two occasions participants will be asked to provide blood samples and given the option of staying overnight at the hospital for these blood samples to be collected. The researchers would expect most patients to be vaccinated against COVID-19 and all precautions will be in keeping with guidance at the time for hospital attendances.
Stage 2: Participants may be required to attend the clinic more often than people who are not in the study. This is because the research staff may want to see them more often to check on progress.
On up to four occasions participants will be asked to provide blood samples and given the option of staying overnight at the hospital for these blood samples to be collected. The researchers would expect most patients to be vaccinated against COVID-19 and all precautions will be in keeping with guidance at the time for hospital attendances. Before they start the trial, and on day 14, participants will have either a CT or an MRI scan of the brain. If participants have CT scans, this uses ionising radiation (x-rays). Ionising radiation may cause cancer many years or decades after the exposure but the chance of this happening is extremely small. If participants have the MRI scan, this can be noisy and claustrophobic. The MRI scan may require the injection of a contrast agent into a vein to allow the cancer to be better seen. This may cause side effects in a small minority of participants.

Where is the study run from?
Scottish Clinical Trials Research Unit (UK)

When is the study starting and how long is it expected to run for?
August 2019 to October 2025

Who is funding the study?
National Institute for Health Research (NIHR) (UK)

Who is the main contact?
PROSSPER trial manager, phs.prossper@phs.scot

Contact information

Type(s)
Public

Contact name
Dr Prossper Study Team

Contact details
SCTRU
1st Floor, Gyle Square
1 South Gyle Crescent
Edinburgh
United Kingdom
EH12 9EB
+44 (0)131 275 7058
phs.prossper@phs.scot

Type(s)
Scientific

Contact name
Prof Chris Twelves

Contact details
St James' University Hospital
Bexley Wing, Level 4
Beckett Street
Leeds
United Kingdom
LS9 7TF
+44 (0)113 206 8186
C.J.Twelves@leeds.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2021-003171-34

Integrated Research Application System (IRAS)
1004104

Central Portfolio Management System (CPMS)
51758

Study information

Scientific Title
PROgesterone as a Steroid SParing agent against oEdema occurring with secondary bRain cancers (PROSSPER)

Acronym

PROSSPER

Study objectives
To establish the optimal dose of oral progesterone to give and to determine if such a dose is safe and well-tolerated by patients.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 16/12/2021, East of England - Cambridgeshire and Hertfordshire Research Ethics Committee (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, United Kingdom; +44 (0)207 104 8096, +44 (0)207 104 8102, +44 (0)207 104 8265; cambsandherts.rec@hra.nhs.uk), ref: 21/EE/0262

Primary study design
Interventional

Study design
Interventional; Design type: Treatment, Drug, Randomized

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Oedema occurring with secondary brain cancers

Interventions
Current interventions as of 27/02/2024:
Stage 1: Participants will receive a single oral dose of micronised progesterone 200 mg on Day 1 and a second single 600 mg dose 5 -21 days later. Blood samples will be collected to measure drug levels after each dose of progesterone. Participants will also receive dexamethasone as non IMP. The daily dexamethasone dose will be the same on both sampling days, but can be adjusted as clinically indicated between the sampling days.

Stage 2: Participants will receive oral micronised progesterone/placebo three times a day (t.d.s.) and an 8 mg/day starting dose of dexamethasone. The progesterone or placebo will only be taken daily for 14 days. The dose of dexamethasone will be reduced over 14 days where possible. The treating clinician will advise the dose to take each day. Blood samples will be collected to measure drug and hormone levels; participants will also be asked to complete questionnaires and an interview.

Previous interventions:
Stage 1: Participants will receive a single oral dose of micronised progesterone 200 mg on Day 1 and a second single 600 mg dose 5 -10 days later. Blood samples will be collected to measure drug levels after each dose of progesterone. Participants will also receive an 8 mg dexamethasone dose on Day 1 but this will be reduced as clinically indicated on other days.

Stage 2: Participants will receive oral micronised progesterone/placebo three times a day (t.d.s.) and an 8 mg/day starting dose of dexamethasone. The progesterone or placebo will only be taken daily for 14 days. The dose of dexamethasone will be reduced over 14 days where

possible. The treating clinician will advise the dose to take each day. Blood samples will be collected to measure drug and hormone levels; participants will also be asked to complete questionnaires and an interview.

Intervention Type
Biological/Vaccine

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Progesterone

Primary outcome(s)
Current primary outcome measure as of 27/02/2024:
Stage 1:
>4 of 6 patients achieve a serum progesterone exposure (area under the concentration/time curve) of 50 – 150% of the target exposure. This will be measured in each patient on two occasions (day 1 and another day between days 5-21) using liquid chromatography-triple quadrupole mass spectrometry (LC/MS/MS) to estimate drug concentrations in eight timed blood samples.

Stage 2:
1. >13 of 18 patients able to tolerate micronised progesterone until the end of the 14-day treatment period at a dose predicted to achieve the target progesterone exposure. This will be measured in each patient on days 1, 8 and 14 using liquid chromatography-triple quadrupole mass spectrometry (LC/MS/MS) to estimate drug concentrations, each at a single timepoint (Ctrough).
2. Trough progesterone concentrations within 50 – 150% of target. This will be measured in each patient on days 1, 8 and 14 using liquid chromatography-triple quadrupole mass spectrometry (LC/MS/MS) to estimate drug concentrations, each at a single timepoint (Ctrough)

Previous primary outcome measure:
Stage 1:
>4 of 6 patients achieve a serum progesterone exposure (area under the concentration/time curve) of 50 – 150% of the target exposure. This will be measured in each patient on two occasions (day 1 and another day between days 5-10) using liquid chromatography-triple quadrupole mass spectrometry (LC/MS/MS) to estimate drug concentrations in eight timed blood samples.

Stage 2:
1. >13 of 18 patients able to tolerate micronised progesterone until the end of the 14-day treatment period at a dose predicted to achieve the target progesterone exposure. This will be measured in each patient on days 1, 8 and 14 using liquid chromatography-triple quadrupole mass spectrometry (LC/MS/MS) to estimate drug concentrations, each at a single timepoint (Ctrough).
2. Trough progesterone concentrations within 50 – 150% of target. This will be measured in each patient on days 1, 8 and 14 using liquid chromatography-triple quadrupole mass spectrometry (LC/MS/MS) to estimate drug concentrations, each at a single timepoint (Ctrough)

Key secondary outcome(s)

Secondary outcome measures:
1. Compliance with the structured dexamethasone dose reduction guidelines at 75% of decision points in at least 13 of 18 patients in line with protocol guidelines and as clinically appropriate. This will be measured by comparing the actual timing of dexamethasone dose reduction to that planned in the protocol at the specified timepoints after each patient has completed stage 2 (22 days duration)
2. Description of dexamethasone-related symptoms and quality of life measured by completion of a patient diary (days 1-22) and the quality of life (QoL) questionnaires DSQ-C, EORTC QLQ-C30 and EORTC BN20 (day 1 and day 14)
3. Percentage of patients achieving a >50% reduction in dexamethasone dose taken on Day 14 , measured by comparing dexamethasone dose at Day 1 and Day 14 in the two patient groups (progesterone and placebo)
4. Comparison of final dexamethasone dose on Day 14 measured by comparing dexamethasone dose at Day 1 and Day 14 in the two patient groups (progesterone and placebo)

Tertiary outcome measures:
1. Confirmation that patients on micronised progesterone have no additional clinically significant changes in their endocrine, liver function or lipid profile. This will be measured by comparison of laboratory data on Days 1, 8, 14 and 22
2. Description of changes on CT/MRI in patients on micronised progesterone compared to those on placebo. CT/MRI will be conducted at screening and Day 14
3. Acceptability/feasibility of PROMs and future trial design, including randomisation, established through patient interviews. This will be measured after each patient has completed stage 2 (22 days duration)

Completion date
01/10/2025

Reason abandoned (if study stopped)
Participant recruitment issue

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 27/02/2024:
1. Patients ≥18 years old
2. Capable of giving informed consent
3. ECOG performance status 0, 1 or 2
4. Diagnosis of cerebral metastases
5. Receiving dexamethasone for control of brain tumour symptoms
6. Ability to swallow oral medication

Previous participant inclusion criteria:
1. Patients ≥18 years old
2. Capable of giving informed consent
3. Eastern Cooperative Oncology Group (ECOG) performance status 0, 1 or 2
4. Clinical and/or radiological diagnosis of cerebral metastases with peri-tumoural oedema on CT /MRI in the last 14 days
5. Responding symptomatically to dexamethasone for control of brain tumour symptoms at a dose of >8 mg for >48 hours
6. Ability to swallow oral medication

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Total final enrolment
6

Key exclusion criteria
Current participant exclusion criteria as of 27/02/2024:
1. Patients who are unable or unwilling to give informed consent
2. History of unexplained vaginal bleeding
3. Concurrent meningioma
4. On HRT medication
5. History of cholestasis in the last 6 months
6. History of allergy to either progesterone or other ingredients of the trial drug including peanut allergy
7. Pregnant or lactating (all female patients of childbearing age will undergo pregnancy testing enrolment (Stage 1)/ randomisation (Stage 2)
8. Clinically significant co-morbidities that in the opinion of the investigator would preclude study participation
9. * Planned surgery, chemotherapy, or radiotherapy within the study treatment period
*Stage 2 only. In Stage 1 there is no tumour assessment so the second micronized progesterone dose (with dexamethasone and pharmacokinetic sampling) can be after any local treatment provided the interval between trial dosing days is no more than 21 days

10. Patients participating in Stage 1 will not be eligible for Stage 2

Previous participant exclusion criteria:
1. Patients who are unable or unwilling to give informed consent
2. History of unexplained vaginal bleeding
3. Concurrent meningioma
4. On HRT medication
5. History of venous thromboembolic disease, myocardial infarction or stroke in last 12 months
6. History of cholestasis in the last 6 months
7. History of allergy to either progesterone or other ingredients of the trial drug including peanut allergy.
8. Pregnant or lactating (all female patients of childbearing age will undergo pregnancy testing prior to randomisation)
9. Clinically significant co-morbidities that in the opinion of the investigator would preclude

study participation
10. Planned surgery, chemotherapy or radiotherapy within the 14-day study treatment period
11. Patients participating in Stage 1 will not be eligible for Stage 2

Date of first enrolment
20/10/2022

Date of final enrolment
01/07/2025

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
St James's University Hospital
Beckett Street
Leeds
United Kingdom
LS9 7TF

Study participating centre
Clatterbridge Cancer Centre
65 Pembroke PLACE
Liverpool
United Kingdom
L7 8YA

Sponsor information

Organisation
Public Health Scotland

ROR
https://ror.org/023wh8b50

Funder(s)

Funder type
Government

Funder Name
NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC); Grant Codes: NIHR130966

Results and Publications

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

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No