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The PIONEER Study - A study to investigate whether taking the medication Pravastatin reduces the number of babies born too early (preterm, i.e., before 37 weeks of pregnancy) and, if so, how it works in the body to do this.

Submission date
17/02/2024

Recruitment status
Recruiting

Registration date
18/04/2024

Overall study status
Ongoing

Last Edited
07/10/2024

Condition category
Pregnancy and Childbirth

[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
Around 7 out of every 100 UK babies are born too early (preterm, i.e., before 37 weeks of pregnancy). Being born preterm is the most common cause of babies dying before the age of one year in the UK; 1 in 3 of those who survive are diagnosed with cerebral palsy. This study will test whether the medicine Pravastatin reduces the number of babies born preterm. It is not fully understood why some babies are born early, and there are few effective treatments to prevent this from happening. Research shows it is likely that early labour may occur because of types of inflammation in the mother's body. Taking a medication which reduces inflammation, such as Pravastatin, could therefore reduce the number of babies being born preterm. Pravastatin has been tested for the treatment and prevention of other pregnancy problems, with no safety concerns for women or their babies, and some studies suggest that it may reduce the number of babies born preterm. This study will test whether taking one tablet of Pravastatin once a day, from between 16-20 weeks of pregnancy until 37 weeks, reduces the number of babies born too early.

Who can participate?
Young and adult women aged 16 years old and over who attend Preterm Birth Prevention clinics

What does the study involve?
Participants will be asked if they would like to join the study. If they join, half will be given Pravastatin and half will be given a placebo (a dummy tablet which looks like Pravastatin but does not contain Pravastatin). Neither the women nor the researchers will know which tablets they are taking until the end of the study. The study will record how many weeks of pregnancy their babies are born and compare this between the two groups of women. The study will also measure levels of certain bacteria and markers of inflammation, which may be related to babies being born early, by collecting blood, fluid produced in the vagina and stool samples. Any

complications the women or their babies have will be recorded and the babies' development will be assessed at two years of age.

What are the possible benefits and risks of participating?
There is a possibility that participants who receive Pravastatin will have a lower chance of preterm birth, but we cannot be certain. This is what this study will help us to find out. If Pravastatin does have this effect, the research could help us to improve the options for pregnant women who are at risk of preterm birth in the future. Participants may also benefit from the increased contact that comes with being a part of a clinical study.

The potential risks and burdens for the trial are summarised in the Participant Information Sheet (PIS), which has been reviewed and approved by our public contributors.
• Possible side effects from the trial medication. These are explained in the PIS, including how likely they are to occur, with clarity that side effects relate to the participant and not their baby.
• Discomfort or pain when having a blood sample taken. Localised bruising and discomfort can occur at the site of venipuncture. Infrequently fainting may occur. Blood samples must be taken from all participants to confirm eligibility and at 28 weeks to assess liver transaminase levels (ALT or AST) - additional blood samples will be taken from all participants at sites taking part in the mechanistic sub-study. Samples will be taken by trained phlebotomists and every effort will be made to reduce pain or discomfort.
• Mild discomfort when having a vaginal swab taken (only participants in the mechanistic sub-study). This will be done by trained clinical staff who are experienced in taking these swabs and will be conducted in such a manner as to maintain privacy and dignity.
• Loss of participant's time to attend research visits at the hospital, take part in qualitative interviews or complete follow-up at home. Trial activities will be integrated into usual care visits where possible to reduce the burden of participation, and researchers will make efforts to arrange visits/calls for convenient times. Participants will also be reimbursed for some expenses.

Where is the study run from?
University Hospitals Bristol and Weston NHS Foundation Trust

When is the study starting and how long is it expected to run for?
February 2024 to February 2028

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

Who is the main contact?
pioneer-trial@bristol.ac.uk

Study website
https://bristol-trials-centre.bristol.ac.uk/details-of-studies/pioneer/

Contact information

Type(s)
Scientific, Principal Investigator

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Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1007563

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
OG/2022/7409, IRAS 1007563, CPMS 60531

Study information

Scientific Title
PravastatIn tO preveNt prEtErm biRth (PIONEER): a parallel group randomised placebo-controlled trial

Acronym
PIONEER

Study objectives

We are interested to find out whether treatment with a statin, Pravastatin, reduces the chance a person will have a preterm birth by extending the length of pregnancy and so reducing the risks associated with babies being born too soon.

We would also like to find out how Pravastatin might work to reduce preterm birth by looking at blood samples, vaginal swabs and stool samples taken from some of the pregnant people who take part in the trial.
We will also see whether Pravastatin has an effect on a number of outcomes which have been selected as being important to this population. Some of these relate to the mother, for example whether they had an infection after birth, and some relate to the child, for example did they need to go to intensive care after birth.
Finally, we will ask some of the people who take part in the trial to complete a questionnaire when their child is 2 years old, to look at the childs' development.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 16/04/2024, North West - Greater Manchester Central Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; None provided; gmcentral.rec@hra.nhs.uk), ref: 24/NW/0074

Study design
Interventional double-blind randomized parallel group placebo-controlled trial

Primary study design
Interventional

Secondary study design
Randomised parallel trial

Study setting(s)
Hospital

Study type(s)
Safety, Efficacy

Participant information sheet

Health condition(s) or problem(s) studied
Intermediate or high risk for preterm birth

Interventions
Participants will be randomised in a 1:1 ratio to receive either Pravastatin or placebo. Randomisation will be performed via the trial database using Sealed Envelope.
Participants randomised to the intervention group will receive Pravastatin 20mg and participants randomised to the placebo group will receive a matched tablet with no active substance. Both will be taken orally once daily by participants, from between 16+0 and 20+0 weeks gestation until 37+0 weeks gestation. Treatment may be stopped earlier (reasons are detailed in the protocol).
All participants will be followed up until birth or loss of pregnancy. Participants recruited in the

first 18 months of the trial will be asked to complete a questionnaire when their child is two years old.

Intervention Type
Drug

Pharmaceutical study type(s)
Pharmacodynamic, Prophylaxis, Therapy, Others (Qualitative evaluation - aims to explore any challenges or obstacles for recruitment and to optimise unbiased trial information delivery to ensure full informed consent is standardised at all sites.)

Phase
Phase III

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

Primary outcome measure
Gestational age, in days, at birth, measured using patient records.

Secondary outcome measures
1. Maternal and neonatal secondary outcomes:
Maternal secondary outcomes: maternal mortality; antenatal infection requiring antibiotics; intrapartum infection requiring antibiotics; development of pre-eclampsia; PPROM; harm to mother from intervention; cervical cerclage; progesterone use; shortest cervical length measured.
Neonatal secondary outcomes: Premature birth (categorising <37 weeks' gestation, and <34 weeks gestation); Apgar scores at 1, 5, and 10 minutes of age; admission to Neonatal Intensive Care Unit (NICU); birthweight; early neurodevelopmental morbidity; gastrointestinal and respiratory morbidity; neonatal mortality; infection requiring antibiotics; need for respiratory support; harm to offspring from intervention. Collected from hospital databases following birth and discharge from hospital admission.
2. Mechanism of action of Pravastatin, evaluated using mechanistic studies to assess maternal:
2.1. Cervicovaginal fluid concentrations of inflammatory markers of interest, including IL-8, IL-6, IL-2, MBL, IgG1, IgG3, C3b and C5a;
2.2. Vaginal microbiota profile;
2.3. Serum lipid profile: very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) assessed via NMR metabolomics; and,
2.4. Stool microbiota profile and metabolomics profile.
2.5. Maternal blood inflammatory profile.
Samples collected as baseline, 24 weeks' gestation and 28 weeks' gestation.
3. For the offspring of pregnancies for those participants recruited during the first 18 months of the trial only. Assessment of child's cognitive and language development using the Parent Report of Children’s Abilities-Revised (PARCA-R) questionnaire. Questionnaire completed at 2 years corrected age for child.

Overall study start date
15/02/2024

Completion date

29/02/2028

Eligibility

Key inclusion criteria
1. Pregnant people with a singleton pregnancy identified as being at high or intermediate risk for PTB according to criteria detailed in the Saving Babies' Lives Care Bundle (V3), where:
1.1. High risk - at least one of the following:
1.1.1. Previous mid-trimester loss >16 weeks' gestation;
1.1.2. Previous PTB <34 week's gestation;
1.1.3. Previous Preterm Premature Rupture of Membranes (PPROM) <34 weeks' gestation;
1.1.4. Previous use of cervical cerclage;
1.1.5. Known uterine structural variant;
1.1.6. Intrauterine adhesions;
1.1.7. History of trachelectomy (for cervical cancer).
OR
1.2. Intermediate risk - at least one of the following:
1.2.1. Previous birth by caesarean section at full dilatation;
1.2.2. History of significant excision of cervical cells (e.g., Large Loop Excision of Transformation Zone (LLETZ) where >15mm depth removed, or >1 LLETZ procedure carried out or cone biopsy).
2. Between 16+0- and 20+0 weeks' gestation at randomisation.

Participant type(s)
Patient

Age group
Mixed

Lower age limit
16 Years

Sex
Female

Target number of participants
750

Key exclusion criteria
1. Multiple pregnancy
2. <16 years of age
3. Hypersensitivity to Pravastatin (active substance or any of the excipients)
4. Personal or first-degree relative with heritable muscle disorder
5. Participating in the active phase of another CTIMP
6. Lactose intolerance
7. >14 units alcohol/week
8. Past/current liver disease
9. ALT or AST above upper limit of normal (as set by local laboratories), to be taken at the time of screening*
10. Bilirubin above upper limit of normal (as set by local laboratories), to be taken at the time of screening*
11. Creatine Kinase (CK) concentration >5 times upper limit of normal (as set by local

laboratories), to be taken at the time of screening
12. Currently breastfeeding
13. Unable to provide informed consent
14. Previously participated in PIONEER
15. Currently taking medicines or groups of medicines that are contraindicated for concomitant use with pravastatin§

* It is acknowledged that the Liver Function Test may include different assessments at different sites, therefore for the purpose of the screening blood test, the term “Liver Function Test” at screening should include measurement of Bilirubin and at least one of ALT or AST. If any of these are above the upper limit of the normal, the person would not be eligible for inclusion in PIONEER, and should have ongoing follow-up according to local policy.
§ Those taking macrolides should be excluded from PIONEER, however, if a limited course of macrolides are prescribed with the course due to complete prior to 20+0 weeks’ gestation, then it may be possible to recruit to PIONEER following completion of the course of antibiotics (if completion of the course of antibiotics is prior to 20+0).

Date of first enrolment
01/11/2024

Date of final enrolment
31/03/2027

Locations

Countries of recruitment
United Kingdom

Study participating centre
Birmingham Womens Hospital
Womens Health Care
Mindelsohn Way
Birmingham
United Kingdom
B15 2TG

Study participating centre
St Michaels Hospital
Southwell Street
Bristol
United Kingdom
BS2 8EG

Study participating centre

Southmead Hospital
Southmead Road
Westbury-on-trym
Bristol
United Kingdom
BS10 5NB

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

Study participating centre
University Hospital (coventry)
Clifford Bridge Road
Coventry
United Kingdom
CV2 2DX

Study participating centre
St Thomas' Hospital
Westminster Bridge Road
London
United Kingdom
SE1 7EH

Study participating centre
Jessops Wing
Royal Hallamshire Hospital
Glossop Road
Sheffield
United Kingdom
S10 2JF

Study participating centre
Hammersmith Hospital
Du Cane Road
Hammersmith

London
United Kingdom
W12 0HS

Study participating centre
The Royal Infirmary of Edinburgh
51 Little France Crescent
Edinburgh
United Kingdom
EH16 4SA

Study participating centre
West Cumberland Hospital
Homewood
Hensingham
Whitehaven
United Kingdom
CA28 8JG

Study participating centre
Norfolk and Norwich University Hospital
Colney Lane
Colney
Norwich
United Kingdom
NR4 7UY

Study participating centre
Birmingham Heartlands Hospital
Bordesley Green East
Bordesley Green
Birmingham
United Kingdom
B9 5SS

Study participating centre
Princess Anne Hospital
Coxford Road
Southampton
United Kingdom
SO16 5YA

Study participating centre
Royal Devon and Exeter Hospital
Royal Devon & Exeter Hospital
Barrack Road
Exeter
United Kingdom
EX2 5DW

Study participating centre
St. Richards Hospital
Spitalfield Lane
Chichester
United Kingdom
PO19 6SE

Study participating centre
Cumberland Infirmary
Newtown Road
Carlisle
United Kingdom
CA2 7HY

Study participating centre
The James Cook University Hospital
Marton Road
Middlesbrough
United Kingdom
TS4 3BW

Study participating centre
Burnley General Hospital
Casterton Avenue
Burnley
United Kingdom
BB10 2PQ

Study participating centre

St Marys Hospital
Oxford Road Site
Manchester
United Kingdom
M13 9WL

Study participating centre
Wythenshawe Hospital
Southmoor Road
Wythenshawe
Manchester
United Kingdom
M23 9LT

Study participating centre
Royal Oldham Hospital
Rochdale Road
Oldham
United Kingdom
OL1 2JH

Study participating centre
John Radcliffe Hospital
Headley Way
Headington
Oxford
United Kingdom
OX3 9DU

Study participating centre
Bradford Royal Infirmary
Duckworth Lane
Bradford
United Kingdom
BD9 6RJ

Study participating centre
University College London Hospital
235 Euston Road

London
United Kingdom
NW1 2BU

Study participating centre
University Hospital of Wales
Heath Park
Cardiff
United Kingdom
CF14 4XW

Sponsor information

Organisation
University Hospitals Bristol and Weston NHS Foundation Trust

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United Kingdom
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+44 (0)117 342 0233
R&DSponsorship@uhbw.nhs.uk

Sponsor type
University/education

Website
https://www.uhbristol.nhs.uk/research-innovation/

Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

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. Internal report
3. Conference presentation
4. Publication on website
5. Submission to regulatory authorities
6. Other

Data will not be made available for sharing until after publication of the main results of the trial. It is the trial team's intention to share underpinning research data in order to maximise reuse and evidence findings. The data will be deposited at the University of Bristol Research Data Repository (data.bris.ac.uk/data) where, once published, they will be assigned a doi: . A metadata record will be published openly by the repository and this record will clearly state how data can be accessed by bona fide researchers.
Anonymised recruitment consultation and interview transcripts may also be used to support teaching of qualitative research methods. We will store audio recordings, transcripts, and written feedback for 25 years, on secure University of Bristol servers. We will make transcripts “Controlled Access”. The anonymised transcripts will be stored in an online database and only made available to other researchers who secure the necessary approvals. All data will be anonymised before they are made available.
Access to the final trial dataset
Anonymous research data will be stored securely and kept for future analysis. Members of the TMG will develop a data sharing policy consistent with University of Bristol policy. Requests for access will be directed to the Research Data team at Bristol, who will assess the motives of potential data re-users before granting access to the data.

Intention to publish date
31/07/2029

Individual participant data (IPD) sharing plan
The datasets generated during the current trial will be available upon request after publication of the main results of the trial. The trial team intends to share underpinning research data to maximise reuse and evidence findings. The datasets will be deposited at the University of Bristol Research Data Repository (https://data.bris.ac.uk/data/) where, once published, they will be assigned a doi. A metadata record will be published openly by the repository and this record will clearly state how data can be accessed by bona fide researchers. The consent form for the trial includes the optional statement: “I agree to my information being stored securely and used for future research and training purposes. I understand that information shared will not include

personally identifiable data.” As such, data will only be deposited from participants who agree to this statement.

IPD sharing plan summary

Stored in publicly available repository, Available on request