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Study to determine the preventive effect of denosumab on breast cancer in women carrying a BRCA1 germline mutation

Submission date 14/09/2022	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 09/11/2022	**Overall study status** Ongoing	
Last Edited 06/03/2026	**Condition category** Cancer	

Plain English summary of protocol

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-denosumab-and-the-risk-of-breast-cancer-in-women-with-changes-to-the-brca1-gene

Background and study aims
This is a preventional later-stage clinical trial in patients with breast cancer. The primary aim is to establish if there is a reduction in the risk of any invasive or ductal carcinoma in situ (occurring inside a milk duct of the breast) breast cancer in women with a germline BRCA1 mutation, a harmful gene variant that can be inherited from either parent when they are treated with the cancer drug denosumab compared to a dummy control drug (placebo).

Who can participate?
Women aged between 25 and 55 years old with a confirmed BRCA 1 germline deletion or likely deletion mutation

What does the study involve?
The study duration is projected to be a total of 12 years, comprising a 2-year enrolment phase, a 5-year treatment phase and a 5-year follow-up phase. The target recruitment is 2918 participants. Once consented, participants will be randomised in a 1:1 ratio using an interactive voice and/or web-based response system. Arm A will be treated with: Denosumab 120 mg by injection under the skin, every 6 months for a duration of 5 years. Arm B will be treated with the placebo comparator with the same routine.

Participation in the study will involve a screening/consent visit followed by treatment visits every 6 months for a duration of 5 years. Participants will then be followed up every 12 months for 5 years after the point that the last investigation product is administered.

What are the possible benefits and risks of participating?
The blood tests could cause pain and bruising. Only nurses experienced in phlebotomy will take blood samples in this study.
Denosumab may cause side effects which are listed in the PIS as follows:

Very Common side effects (which may affect more than 1 person in 10):
1. Low blood calcium
2. Shortness of breath
3. Muscle and bone pain
Common side effects (which may affect between 1 and 10 people in every 100):
1. Decreased phosphorus in the blood
2. Osteonecrosis of the jaw
3. Hair loss (alopecia)
Uncommon effects (which may affect between 1 and 10 people in every 1,000):
1. High blood calcium in patients with Giant Cell Tumor of Bone (GCTB) after stopping denosumab
2. Unusual thigh bone fracture (atypical femoral fracture
3. Rash that may occur on the skin or sores in the mouth (lichenoid drug eruption)
Rare side effects (which may affect between 1 and 10 people in every 10,000):
1. Allergic reaction (drug hypersensitivity)
2. Broken bones in your spine after stopping Denosumab

Where is the study run from?
Manchester University Hospital NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
June 2022 to June 2032

Who is funding the study?
1. Austrian Breast and Colorectal Cancer Study Group (ABCSG) (Austria)
2. Amgen (USA)
3. US Department of Defense (USA)

Who is the main contact?
Oncology Research Team, MFT.OncologyResearch@nhs.net (UK)

Contact information

Type(s)
Principal investigator, Scientific

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT05382286

Clinical Trials Information System (CTIS)
2017-002505-35

Integrated Research Application System (IRAS)
1005699

Central Portfolio Management System (CPMS)
54435

Protocol serial number
B00782

Study information

Scientific Title
BRCA-P: A randomized, double-blind, placebo-controlled, multi-center, international phase III Study to determine the preventive effect of denosumab on breast cancer in women carrying a BRCA1 germline mutation

Acronym
BRCA-P

Study objectives
To evaluate the reduction in the risk of any breast cancer (invasive or DCIS) in women with germline BRCA1 mutation who are treated with denosumab compared to placebo

To determine the reduction in the risk of invasive breast cancer in women with germline BRCA1 mutation who are treated with denosumab compared to placebo
To determine the reduction in the risk of invasive triple negative breast cancer (TNBC) in women with germline BRCA1 mutation who are treated with denosumab compared to placebo
To determine the reduction in risk of ovarian, fallopian and peritoneal cancers (in women who have not undergone PBSO) in women with germline BRCA1 mutation who are treated with

denosumab compared to placebo
To determine the reduction in risk of other (i.e. non-breast and non-ovarian) malignancies, including those known to be associated with BRCA1 germline mutations in women with germline BRCA1 mutation who are treated with denosumab compared to placebo
To determine the reduction in the risk of clinical fractures in pre- and postmenopausal women with germline BRCA1 mutation who are treated with denosumab compared to placebo

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 13/09/2022, Health and Care Research Wales (Address: not available; Tel: not available; HCRW.approvals@wales.nhs.uk, approvals@hra.nhs.uk), ref: 22/WA/0204

Primary study design
Interventional

Study design
Randomized placebo-controlled double-blind multi-centre prospective study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Breast cancer

Interventions
Arm A (Experimental): Denosumab 120 mg subcutaneously, every 6 months (q6m) for 5 years. (Daily supplements, containing 500 mg elemental calcium and at least 400 I.U. vitamin D are highly recommended throughout the study treatment).
Arm B (Placebo Comparator): Placebo sc, q6m for 5 years (Daily supplements, containing 500 mg elemental calcium and at least 400 I.U. vitamin D are highly recommended throughout study treatment).

Intervention Type
Drug

Phase
Phase III

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

Primary outcome(s)
Follow-up visits should be performed either as a clinic visit, telephone contact, email or other means of communication yearly.
1. Quality of Life measured using the self-reported questionnaires SF-12, Cancer Worry Scale, Impact of Events Scale (IES) and the Greene Climacteric Scale, (provided to perimenopausal /postmenopausal participants only), as well as a BRCA-P questionnaire provided to the participant at the following treatment visits: 6 months, 12 months, and every 12 months after that

2. Adverse events, fractures, oncologic events and oral events (ONJ) should be collected either by clinic visit, telephone contact, email or other means of communication at the end of treatment visit/contact, 6 months after the participant received the last dose of IP
3. Occurrence of new oncological events obtained from the participant and recorded in study records at each yearly follow-up visit/contact

Key secondary outcome(s)
1. Occurrence of new clinical fractures and whether a diagnostic x-ray was performed obtained from the participant and recorded in study records at each yearly follow-up visit/contact
2. Atypical Femur Fracture occurrence proactively assessed during each clinical visit, phone or email contact and recorded in the participant's study records
3. Osteonecrosis of the Jaw Assessment (ONJ) proactively assessed during each clinical visit, phone or email contact and recorded in the participant's study records
4. Osteonecrosis of the external auditory canal proactively assessed during each clinical visit, phone or email contact and recorded in the participant's study records

Completion date
01/06/2032

Eligibility

Key inclusion criteria
1. Women with a confirmed deleterious or likely deleterious BRCA 1 germline mutation (Variant class 4 or 5)
2. Age ≥25 years and ≤55 years at randomization
3. No evidence of breast cancer by MRI or MG and clinical breast examination within the last 6 months prior to randomization
4. No clinical evidence of ovarian cancer at randomization
5. Negative pregnancy test at randomization for women of childbearing potential
6. Documentation that preventive breast surgery has been discussed as a potential treatment but is not planned at the time of randomization
7. Women for whom preventive medications (tamoxifen, raloxifene or aromatase inhibitors) are not indicated as the standard of care, or who have an intolerance of or opt not to take these drugs.
8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
9. Written informed consent before any study-specific procedure is performed

All individuals will be considered for inclusion in this study regardless of disability, marriage and civil partnership, maternity, race, religion and belief, and sexual orientation.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
25 Years

Upper age limit
55 Years

Sex
Female

Total final enrolment
3

Key exclusion criteria
1. Prior bilateral mastectomy
2. History of ovarian cancer (including fallopian tube and primary peritoneal cancer)
3. History of breast cancer
4. History of invasive cancer except for basal cell or squamous cell skin cancer. History of the following are also allowed: carcinoma in situ of the cervix, stage 1 papillary or follicular thyroid cancer, atypical hyperplasia or LCIS (Lobular Carcinoma In Situ)
5. Pregnant or lactating women (within the last 2 months prior to randomization)
6. Unwillingness to use highly effective contraception method during and within at least 5 months after cessation of denosumab/placebo therapy in women of childbearing potential.
Clinically relevant hypocalcaemia (history and current condition), or serum calcium <2.0 mmol/L (<8.0 mg/dL)
Hypocalcemia defined by calcium below the normal range (a single value below the normal range does not necessarily constitute hypocalcemia, but should be 'corrected' before dosing the participant). Monitoring of calcium level in regular intervals (usually prior to IP administration) is highly recommended
7. Tamoxifen, raloxifene or aromatase inhibitor use during the last 3 months prior to randomization or for a duration of more than 3 years in total (current and prior HRT is permitted)
8. Prior use of denosumab
9. Participant has a known prior history or current evidence of osteonecrosis or osteomyelitis of the jaw, or an active dental/jaw condition which requires oral surgery including tooth extraction within 3 months of enrollment
10. Concurrent treatment with a bisphosphonate or an anti-angiogenic agent
11. Any major medical or psychiatric condition that may prevent the participant from completing the study
12. Hepatic impairment (defined as known chronic liver disease such as alcoholic cirrhosis or chronic autoimmune hepatitis or transaminases (aspartate aminotransferase or alanine aminotransferase) >1.5x upper limit of the laboratory normal range.
13. Known active infection with Hepatitis B virus or Hepatitis C virus
14. Known infection with human immunodeficiency virus (HIV)Use of any other investigational product (current or prior Aspirin or NSAIDs are permitted)
15. Hypersensitivity to the active substance or to any of the excipients
16. Known rare hereditary problems of fructose intolerance

Date of first enrolment
20/11/2022

Date of final enrolment
31/12/2024

Locations

Countries of recruitment
United Kingdom

Australia

Austria

Germany

Israel

Spain

Study participating centre
Manchester University Hospital NHS Ft (hq)
Oxford Road
Manchester
England
M13 9WL

Sponsor information

Organisation
Manchester University NHS Foundation Trust

ROR
https://ror.org/00he80998

Funder(s)

Funder type
Other

Funder Name
Austrian Breast and Colorectal Cancer Study Group (ABCSG)

Funder Name
Amgen

Alternative Name(s)

Amgen Inc., Applied Molecular Genetics Inc.

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Funder Name
U.S. Department of Defense

Alternative Name(s)
United States Department of Defense, Department of Defense, U.S. Dept of Defense, US Department of Defense, US Dept of Defense, U.S. Department of Defense, Department of War, United States Department of War, War Department, War Office, DOW, DOD, USDOD

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan

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
Protocol file	version 1.0	01/04/2022	06/10/2022	No	No