ISRCTN15516131 https://doi.org/10.1186/ISRCTN15516131

A Phase I/II, open-label, multi-center trial of [177Lu]Lu-NeoB in combination with capecitabine in adult patients with gastrin releasing peptide receptor positive, estrogen receptor-positive, human epidermal growth receptor-2 negative metastatic breast cancer after progression on previous endocrine therapy in combination with CDK4/6 inhibitor

Submission date 20/06/2024	**Recruitment status** Recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 11/09/2024	**Overall study status** Ongoing	
Last Edited 08/10/2024	**Condition category** Cancer	

Plain English summary of protocol

Background and study aims
The purpose of the study is to determine the safest and most appropriate dose and dosing schedule of Lutetium-NeoB in combination with capecitabine in participants with your type of breast cancer. This study will be divided into two parts:
Phase I - Dose Escalation
The dose of the test drug is increased a little at a time in different groups of people until the recommended dose for the next part of the study is found, based on the side effects that patients experience. A dose escalation study may also measure the ways that the drug is used by the body.
Phase II - Dose Optimisation
This part explores the doses identified in part I more, to see if they work against breast cancer and to look more at safety and tolerability.
This study will also explore the safety of the PET imaging agent, Gallium-NeoB, and how well this identifies the GRPR protein that may be found on your breast cancer cells.

Who can participate?
Patients aged 18 years and older with breast cancer

What does the study involve?
The study treatment will comprise two medicines: Lutetium-NeoB is an investigational type of

cancer treatment called radioligand therapy (RLT), which delivers targeted radiation to cancer cells (and minimises radiation to healthy tissue) by binding to the GRPR receptor on the cell surface. The treatment is delivered via a cannula inserted into a vein in the arm and the drug travels through the bloodstream to tumour cells. This typically takes 10 minutes to complete. The second study medicine is capecitabine, which is already an approved medicine for breast cancer. Participants will be in the study for about 6 years (1 year on treatment and 5 years of follow-up). During this time, participants will undergo a variety of tests and procedures. Participants may experience unanticipated side effects from the study treatments and/or procedures done in this trial. The study doctor will keep a close eye on any side effects.

What are the possible benefits and risks of participating?
There are several assessments foreseen within the study period. For these assessments and the treatment, several medical procedures are necessary, and the related risks are described below. To check for side effects, participants will be monitored for up to 6 years from the start of the study. Lutetium-NeoB is an investigational drug, meaning it has not yet been approved by regulatory authorities. Capecitabine is a marketed cancer medication and is regularly used in clinical practice. The risk for patients in this trial will be minimised by compliance with eligibility criteria, study procedures, and dose modification/ stopping criteria, as well as with close clinical monitoring.
Participants may experience side effects from the study treatments and/or procedures, including radiation from the study imaging agent, study treatment, PET/CT or PET/MRI scans, tumour assessments (CT/MRI/whole body bone scan), and SPECT/CT scans. Some imaging procedures e.g. CT/MRI scans to assess tumour response will be performed more frequently during the study than in routine clinical care (in which they would usually be performed less frequently, based on symptoms). Other scans e.g. PET/CT or PET/MRI with the radioactive agent Gallium-NeoB, or radioactivity measurements by SPECT/CT are not a part of standard diagnostic procedures, but will be performed in this study (to assess eligibility/ changes in GRPR expression with treatment and to understand where and how much of the radioactive drug, Lutetium-NeoB is distributed within the body, respectively). Therefore, exposure to radiation in this study will be above the standard of care. Furthermore, the imaging agent and study treatment also contribute to the participant's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk of other tumours.
Side effects related to Gallium-NeoB administration: this PET imaging agent has been shown to be safe in two completed clinical studies and it is currently being used in an ongoing study called NeoRay. So far, 50 participants have received Gallium-NeoB, and no safety concerns related to it have been reported. However, there may be unknown side effects.
The potential risks issued from Lutetium-NeoB are primarily of two types: radioactivity side effects and risks related to the nature of the drug.
The most common side-effects from Lutetium-NeoB are:
1. Decrease of blood cells: red blood cells, platelets (which help the blood to clot), and white blood cells (which help fight infection). Consequently, you may be at risk of bleeding, fatigue, shortness of breath, and infection. This happens in many patients and is frequently temporary. However, sometimes, it is long-standing and/or permanent, which could result in your discontinuation from the clinical trial.
2. The pancreas, kidneys, and bone marrow may be affected. To check the possible adverse effects of treatment with the Lutetium-NeoB on these organs, the function of these organs will be assessed throughout the study duration by taking blood and urine tests.
3. The ovaries or testes may possibly be affected by radioactivity, which may reduce fertility, although this has not been reported with Lutetium-NeoB so far.
4. Other secondary effects could be nausea (feeling sick), vomiting and abdominal pain, usually during the treatment administration and during the first 24 hours.
5. Possible delayed (after the first 24 hours) side effects of the radiation include fatigue and

temporary hair loss.
There is also an inconvenience associated with radioligand therapy, as patients must socially distance from others and follow extra hygiene methods for up to 7 days post-treatment as per the Therapy Discharge Instructions included in this application.
Blood collection risks: As part of this study, you will have samples of your blood collected. The risks of collecting blood may include fainting, pain, and/or bruising, dizziness, and in rare cases, infection. A cream to reduce the discomfort of the needle may be applied ahead of time. Rarely, there may be a small blood clot or infection at the site of the needle puncture or central line.
Intravenous infusion risks: For practical and radioprotection reasons it is often used to insert a cannula (plastic tube a few centimetres long) through the skin into a vein. The insertion will feel like a sharp scratch. The possible risks related to this procedure are infection, inflammation of the vein, blood from blood vessels leaking into surrounding tissue and causing a blood clot.
Tissue sampling risks: A tumour tissue sample will be collected for exploratory biomarker testing during the screening period. This should be a newly obtained biopsy or a piece of a previously collected tumour biopsy. Side effects of having a biopsy include minor local bleeding or pain at the needle site, or swelling under the skin.
Electrocardiogram (ECG) risks: mild irritation, slight redness, and itching.

Where is the study run from?
Novartis (UK)

When is the study starting and how long is it expected to run for?
June 2024 to September 2031

Who is funding the study?
Novartis Pharma (Germany)

Who is the main contact?
Dr Laura Kenny, l.kenny@imperial.ac.uk

Contact information

Type(s)
Scientific

Contact name
Dr Cristiana Balcu

Contact details
Building 4
Uxbridge Business Park
Sanderson Road
Uxbridge
United Kingdom
UB8 1DH
+40 (0)756 014 262
Europe.CTA@Novartis.com

Type(s)
Scientific

Contact name
Dr Natasha Khatwa

Contact details
2nd Floor
The WestWorks Building
White City Place
195 Wood Lane
London
United Kingdom
W12 7FQ
+44 (0)788 499 8747
natasha.khatwa@novartis.com

Type(s)
Principal Investigator

Contact name
Dr Laura Kenny

Contact details
Du Cane Road
London
United Kingdom
W12 0HS
+44 (0)20 3313 1000
l.kenny@imperial.ac.uk

Additional identifiers

EudraCT/CTIS number

IRAS number
1009808

ClinicalTrials.gov number
NCT06247995

Secondary identifying numbers
CAAA603D12101, CPMS 56224

Study information

Scientific Title
A Phase I/II, open-label, multi-center trial of [177Lu]Lu-NeoB in combination with capecitabine in adult patients with gastrin releasing peptide receptor positive, estrogen receptor-positive, human epidermal growth receptor-2 negative metastatic breast cancer after progression on previous endocrine therapy in combination with CDK4/6 inhibitor

Acronym

CAAA603D12101

Study objectives
Phase I: To determine the Recommended Doses (RD) and dosing regimens of [177Lu]Lu-NeoB in combination with capecitabine

Phase II: To evaluate preliminary anti-tumor activity across two randomized cohorts of two different doses/regimens of [177Lu]Lu-NeoB in combination with capecitabine

1. Phase I and Phase II:
To characterize the PK and biodistribution (dosimetry) of [177Lu]Lu-NeoB in combination with capecitabine
2. Phase I and Phase II:
To evaluate the safety and tolerability of the [68Ga]Ga-NeoB
3. Phase I and Phase II:
To evaluate, at the participant level, agreement between [68Ga]Ga-NeoB PET and conventional imaging
4. Phase I only:
To determine the optimal [68Ga]Ga-NeoB radioactivity dose
5. Phase I only:
To evaluate preliminary anti-tumor activity of [177Lu]Lu-NeoB in combination with capecitabine
6. Phase II only:
To evaluate the safety and tolerability of [177Lu]Lu-NeoB in combination with capecitabine

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 10/09/2024, London - Riverside Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 104 8150; riverside.rec@hra.nhs.uk), ref: 24/LO/0511

Study design
Randomized controlled 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
Breast cancer

Interventions
The purpose of this study is to find the dose of a new drug called [177Lu]Lu-NeoB (Lutetium NeoB), when given together with the breast cancer treatment capecitabine and to determine how frequently this drug should be given to women and men who have metastatic breast cancer. Also to learn how safe and effective Lutetium-NeoB is against breast cancer when given together with capecitabine. Capecitabine is an approved medicine. Participants will be in the study for up to about 6 years (1 year on treatment and 5 years of follow-up). The study is expected to run globally until 2031.

In this study, all participants (in phase I and II) will undergo a [68Ga] Ga-NeoB PET/CT or PET/MRI scan during screening to assess GRPR expression. Since the Phase I part of the study also includes dose optimisation for the [68Ga] Ga-NeoB, it is possible that patients who are assigned to dose range 3 100 MBq (range 74-130 MBq) may need to have an additional [68Ga] Ga-NeoB administration and following PET/CT or PET/MRI scan if there is no uptake shown on the first scan (to assess if the lack of uptake was due to the administered radioactivity dose being too low, or due to a lack of GRPR expression). The researchers anticipate this would only affect ~2-3 patients globally (per protocol).

Participants in phase II will undergo an additional [68Ga] Ga-NeoB PET/CT or PET/MRI scan after the end of RLT treatment (4-8 weeks after) to assess the difference of [68Ga] Ga-NeoB PET scan between baseline and end-of-RLT.

In both study phases, either 6 or 12-dose administrations of [177Lu] Lu-NeoB are planned for participants receiving the investigational RLT in a Q6W or Q3W dosing regimen, respectively, unless treatment is discontinued earlier for any reason. However, the protocol does permit additional administrations of [177Lu] Lu-NeoB beyond these 6/12 administrations, if the patient is continuing to derive clinical benefit and they meet the protocol-defined criteria.

Capecitabine at 1000 mg/m2 BID from Day 1 through 14 of a 21-day cycle will be administered until disease progression, unacceptable toxicity, withdrawal of consent, loss to follow-up, Investigator decision or death, whichever occurs first. After the end of treatment, participants will have a safety follow-up for 8 weeks after treatment discontinuation and then long-term safety and survival follow-up for up to 5 years from the date of the participant’s last dose of Lutetium-NeoB.

Intervention Type
Drug

Pharmaceutical study type(s)
Pharmacokinetic, Dose response

Phase
Phase I/II

Drug/device/biological/vaccine name(s)
[177Lu]Lu-NeoB [[177Lu]Lu-NeoB, [68Ga]Ga-NeoB [[68Ga]Ga-NeoB, capecitabine

Primary outcome measure

Phase I:
1. Incidence and severity of AEs including dose-limiting toxicities (DLTs) until 6 weeks, serious adverse events (SAEs) until 8 weeks after the last dose and until the end of the study, respectively, changes in laboratory parameters and vital signs until 8 weeks after the last dose (EOT) and additionally during the follow-up period until disease progression (PD), and ECGs before and after 1st and 3rd administrations, before other administrations and until the last dose of [177Lu]Lu-NeoB
2. Tolerability: dose interruptions, discontinuations, and reductions recorded until the last dose of [177Lu]Lu-NeoB

Phase II:
1. Overall response rate (ORR), clinical benefit rate (CBR), time to response (TTR), duration of response (DOR), progression-free survival (PFS) as per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 by local investigator assessment: every 9 weeks until month 18 then every 12 weeks until month 36 and then as clinically indicated until disease progression or end of the study (EOS)
2. Overall survival (OS): until the end of the study

Secondary outcome measures
1. Phase I and II:
1.1. Time activity curves (TACs) and absorbed radiation doses of [177Lu]Lu-NeoB in organs and tumor lesions: C1D1 (1h-4 h, 24 h, 48 h, 168 h), for Q3W: C3D1, C5D1 and for QW6: C5D1, C9D1
1.2. Concentration of [177Lu]Lu-NeoB in blood over time and derived PK parameters (pre-dose, end of infusion, 0.5, 1, 2, 4, 6, 24, 48, 168 h)
2. Phase I and II:
2.1. Incidence and severity of adverse events following [68Ga]Ga-NeoB administration at screening: within 3 days after screening dose
3. Phase I and II:
3.1. Positive Percent Agreement (PPA) and Positive Predictive Agreement (PPrA) using conventional imaging as reference by central assessment, at screening
4. Phase I only:
4.1. Visual assessment of image quality by central assessment at screening
5. Phase I only:
5.1. ORR, CBR, TTR, DOR, PFS as per RECIST v1.1 by local investigator assessment: every 9 weeks until month 18 then every 12 weeks until month 36, then as clinically indicated until PD or EOS
5.2. OS: until EOS
6. Phase II only:
6.1. Incidence and severity of AEs, SAEs until 8 weeks after EOT, changes in laboratory parameters and vital signs until 8 weeks after EOT and during FU period until PD, and ECGs before and after 1st and 3rd doses, before other doses and until EOT of [177Lu]Lu-NeoB
6.2. Dose interruptions, discontinuations, and reductions recorded until EOT of [177Lu]Lu-NeoB

Overall study start date
10/06/2024

Completion date
09/09/2031

Eligibility

Key inclusion criteria

1. Participant is female or male adult ≥18 years old at the time of informed consent(s)
2. Participant has a histologically and/or cytologically documented diagnosis of ER+ breast cancer (ER expression >10% of tumor cell nuclei stain (regardless of PgR expression) (based on the most recently analyzed tissue sample tested by a local laboratory).
3. Participant has HER2- breast cancer defined as a negative in situ hybridization test (ISH) or an IHC status of 0, 1+ or 2+. If IHC is 2+, a negative ISH (e.g., FISH, CISH, or SISH) (based on the most recently analyzed tissue sample tested by a local laboratory) is required.
4. Participant received no more than three prior endocrine therapy/ies (single agent or in combination with targeted therapy) regimen/s in the metastatic setting of which at least one included endocrine therapy in combination with a CDK4/6i. In addition:
4.1. In case of confirmed presence of deleterious or suspected deleterious germline BRCA1 or BRCA2 mutation, the participant may also have received a PARP inhibitor-based therapy.
4.2. In case of HER2-low breast cancer, the participant may also have received Enhertu®.
Note: disease progression while on adjuvant ET (with or without CDK4/6i) or within 12 months of completing adjuvant endocrine therapy (with or without CDK4/6i), will be considered a line of therapy.
5. Participant has metastatic breast cancer with radiologically confirmed progression of disease after the most recent therapy
6. Participant must have measurable disease, i.e., at least one measurable lesion as per RECIST 1.1. (a lesion at a previously irradiated site may only be counted as a target lesion if there is a clear sign of progression since the irradiation) as per local assessment.
Note: If only lytic bone lesions are present, they must have at least one lesion with a soft tissue component that can be evaluated by CT or MRI and meets the definition of measurability as per RECIST 1.1 criteria (participants with only one predominantly lytic bone lesion that has been previously irradiated are eligible if there is documented evidence of disease progression of the bone lesion after irradiation).
7. Participant has at least one target lesion [as per RECIST 1.1 and based on the baseline contrast-enhanced CT (or MRI)] with [68Ga]Ga-NeoB uptake above the liver at PET/CT or PET /MRI, as per local reading. In addition:
Participant with liver or lung disease involvement must show [68Ga]Ga-NeoB uptake above the liver as follows:
If there is liver disease involvement (in the absence of lung involvement), in ≥ 50% of all CT measurable liver lesions (RECIST 1.1)
If there is lung disease involvement (in the absence of liver involvement), in ≥ 50% of all CT measurable lung lesions (RECIST 1.1)
Participants with both liver and lung disease involvement must show [68Ga]Ga-NeoB uptake above the liver in ≥ 50% of all CT measurable lesions either in liver or lung (RECIST 1.1) and in at least one measurable lesion in the remaining organ (lung or liver)
8. Participant has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
9. Participant has adequate bone marrow and organ function as defined by laboratory values in section 5.1 (as assessed by local laboratory).
10. For Phase I part only: Female participant must be in postmenopausal status at the time of starting study treatment, as defined in Section 5.1
For Phase II part only:
Female participant is post-menopausal as per criteria above at the time of starting study treatment.
Female participant is pre/peri-menopausal at the time of starting study treatment, as defined in Section 5.1

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
66

Key exclusion criteria
1. Participant with symptomatic visceral disease or any disease burden that are at risk of life-threatening complications as per the investigator's judgment.
2. Participant has received prior treatment with chemotherapy in the metastatic setting (allowed in neoadjuvant/ adjuvant setting, unless progression or recurrence occurred during or within 12 months after completion of adjuvant chemotherapy).
3. Participant has received prior treatment with capecitabine
4. Participant has inflammatory breast cancer at screening.
5. Participant has any other concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgment, cause unacceptable safety risks, contraindicate participant participation in the clinical study or compromise compliance with the protocol
6. History or current diagnosis of impaired cardiac function, clinically significant cardiac disease or ECG abnormalities
7. Participant is currently receiving brivudine which cannot be discontinued at least 4-week prior to start of capecitabine therapy.
8. Participant is currently receiving NEP inhibitors (i.e., Entresto®) and images for dosimetry assessments cannot be acquired for this participant as per Section 8.7.3 of the protocol.
9. Participant with known deficiency or family history of deficiency of dihydropyrimidine dehydrogenase.
10. Sexually active male participants unwilling to: remain abstinent (refrain from sexual intercourse) or use a condom, while taking study treatment and for at least 4 months after the last administration of [177Lu]Lu-NeoB, or 3 months after the last dose of capecitabine (or as per locally prescribing information) whichever is longer, in addition to the highly effective method used by the partner who is a female of child-bearing potential.
11. For Phase II part only
11.1. Pregnant or breastfeeding women
11.2. Women of childbearing potential

Date of first enrolment
29/09/2024

Date of final enrolment
21/06/2026

Locations

Countries of recruitment
Australia

Canada

China

France

Germany

Italy

Netherlands

Portugal

Singapore

Spain

United Kingdom

Study participating centre
-
United Kingdom
-

Sponsor information

Organisation
Novartis (United Kingdom)

Sponsor details
2nd Floor
The west works Building
White City Place
195 Wood Lane
London
England
United Kingdom
W12 7FQ
-
natasha.khatwa@novartis.com

Sponsor type
Industry

Website

https://www.novartis.co.uk/

ROR
https://ror.org/039s6n838

Funder(s)

Funder type
Industry

Funder Name
Novartis Pharma

Alternative Name(s)
Novartis Deutschland GmbH, Novartis Pharma GmbH, Novartis Deutschland

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
Germany

Results and Publications

Publication and dissemination plan
Peer-reviewed scientific journals
Internal report
Conference presentation
Publication on website
Submission to regulatory authorities

After the study is completed, a summary of the results will be publicly available at https://www.novartisclinicaltrials.com, https://www.ClinicalTrials.gov, and/or at the European Clinical Trials Database (EudraCT, https://eudract.ema.europa.eu/. The CSR is shared with the Investigators who can then explain/share the results with the patients.

Intention to publish date
09/09/2032

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