Clinical Trial Protocol
Iranian Registry of Clinical Trials

28 May 2026

A Phase III, randomized, two armed, double-blind, parallel, active controlled, non-inferiority clinical trial to compare efficacy and safety of Denosumab (produced by AryoGen Pharmed Co.) versus Denosumab (Xgeva®, produced by Amgen Company) in breast cancer patients with bone metastasis

Protocol summary

Study aim

To verify the non-inferior efficacy of Denosumab (AryoGen) compared with Xgeva® (produced by Amgen) by time to first on-study Skeletal Related Event (SRE) in breast cancer patients with bone metastasis

Design

A phase III, Active-controlled, Parallel, double-blind, randomized clinical trial with 272 patients.

Settings and conduct

A phase III, randomized, two armed, double-blinded, parallel, active-controlled and multicenter clinical trial in Iran

Participants/Inclusion and exclusion criteria

Inclusion: Female patients 18-75 years old, breast adenocarcinoma, Radiographic evidence of at least one bone metastasis, Eastern Cooperative Oncology Group (ECOG) ≤2, Adequate organ function. Exclusion: Planned radiation therapy or bone surgery, Life expectancy <6 months, brain and liver metastasis, Prior administration of Denosumab or IV bisphosphonates, Non-healed dental/oral problem or condition which requires oral surgery, osteonecrosis/osteomyelitis of the jaw, Disorders associated with abnormal bone metabolism, Prior malignancy (other than breast cancer, basal cell carcinoma, or in situ cervical cancer) within 3 years prior to randomization, HIV, HBV, HCV, Receiving any investigational product or device in other clinical trials 30 days prior to the study, Allergy to any of the products, Received calcitonin, Parathyroid hormone related peptides, mithramycin, strontium ranelate, or gallium nitrate within 8 weeks prior to randomization, Any psychiatric disorder, organ disfunction or systemic disease, Pregnancy or breast feeding.

Intervention groups

Control group: Denosumab (Xgeva® produced by Amgen Co), Intervention group: Denosumab (produced by AryoGen pharmed) (Subcutaneous, 120 mg once every 4 weeks for 80 weeks)

Main outcome variables

Assessing the time to first on-study SRE in breast cancer patients with bone metastasis.

General information

Reason for update

According to the comment of the respected referee, the sections related to the exclusion & inclusion criteria were edited.

Acronym

IRCT registration information

IRCT registration number: **IRCT20150303021315N21**
Registration date: **2021-01-06, 1399/10/17**
Registration timing: **prospective**

Last update: **2023-12-05, 1402/09/14**
Update count: **1**

Registration date

2021-01-06, 1399/10/17

Registrant information

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Recruitment status
Recruitment complete
Funding source

Expected recruitment start date
2021-02-03, 1399/11/15
Expected recruitment end date
2023-01-13, 1401/10/23
Actual recruitment start date
empty
Actual recruitment end date
empty
Trial completion date
empty

Scientific title
A Phase III, randomized, two armed, double-blind, parallel, active controlled, non-inferiority clinical trial to compare efficacy and safety of Denosumab (produced by AryoGen Pharmed Co.) versus Denosumab (Xgeva®, produced by Amgen Company) in breast cancer patients with bone metastasis

Public title
Evaluation of efficacy and safety of Denosumab (produced by AryoGen Pharmed Co.) versus Denosumab (Xgeva®, produced by Amgen Co.)
Purpose
Treatment
Inclusion/Exclusion criteria
Inclusion criteria:
Female patients aged 18-75 years old at the time of signing informed consent form ICF History or known case of breast adenocarcinoma Radiographic evidence of at least one bone metastasis Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2. Adequate organ function: Albumin-adjusted serum calcium ≥ 2.0 mmol/L [≥ 8.0 mg/dL] and ≤ 2.9 mmol/L [≤ 11.5 mg/dL], Serum aspartate aminotransferase (AST) ≤2.5 ULN, Serum alanine aminotransferase (ALT) ≤2.5 ULN, Serum total bilirubin ≤2 ULN, Creatinine clearance ≥30 mL/min (stage 1-3 CKD patients), Serum Creatinine ≤1.5 ULN, Leukocytes > 3,000/mcL (without growth factor), Platelets > 100,000/mcL, Hemoglobin ≥8 g/d
Exclusion criteria:
Planned radiation therapy or bone surgery Life expectancy less than 6 months Known brain and liver metastasis Prior administration of Denosumab or IV bisphosphonates Non-healed dental/oral surgery History or current evidence of osteonecrosis/osteomyelitis of the jaw Active dental or jaw condition which requires oral surgery Planned invasive dental procedure in the course of the study Disorders associated with abnormal bone metabolism including uncontrolled hyperthyroidism or hypothyroidism or Paget's disease Prior malignancy (other than breast cancer, basal cell carcinoma, or in situ cervical cancer) within 3 years prior to randomization Known infection with human immunodeficiency virus (HIV) Known infection with Hepatitis B or Hepatitis C virus (HBV or HCV) Receiving any investigational product or device in other clinical trials 30 days prior to the study Allergy to any of the products to be administered during the study (eg, Denosumab, mammalian cell line products, calcium or vitamin D) Treatment with calcitonin, parathyroid hormone-related peptides, mithramycin, strontium ranelate, or gallium nitrate within 8 weeks prior to randomization Any psychiatric disorder, organ disfunction or systemic disease that, in the opinion of the investigator, might prevent the subject from completing the study or interfere with the interpretation of the study results Pregnancy or breast feeding
Age
From **18 years** old to **75 years** old
Gender
Female

Phase
3
Groups that have been masked

- Participant
- Investigator

Sample size
Target sample size: **272**
Randomization (investigator's opinion)
Randomized
Randomization description
Eligible patients will be assigned to treatment with the use of stratification, permuted block (length of each block is 2), and R-CRAN software (version 3.2.3) that will be designed to achieve the overall balance between groups; randomization will be stratified according to prior Skeletal Related Event (SRE), prior oral bisphosphonate use, and current chemotherapy (chemotherapy treatment from 6 weeks prior randomization until the randomization date). After the randomization procedure, a code will be allocated to each patient that will be used as a patient identifier throughout the study. The assigned code will be denoted by 4 initials (corresponding to the 2 first letters of the first name, the 2 first letters of the first surname) and 3 numbers (center code). Moreover, the code is followed by study unique identification consisting of the first three letters of the generic name of the investigational product (which is DEN-) and 3 numbers (corresponding to the randomization number), e.g. ABCD001DEN-001. The randomization number will be assigned in a consecutive way. Each Denosumab drug packages (allocated to each patient's injection) will have an exclusive code. Also, CRO (Contract Research Organization) will monitor the way of patient's drug allocation in treatment groups.
Blinding (investigator's opinion)
Double blinded
Blinding description
The participants, physicians, nurse (for injection) and those who assess the study outcomes will be unaware of the state of the patient with regard to receiving Denosumab (AryoGen) or Denosumab (Xgeva®). The drug packaging type is vial, therefore the drug will be exclusively prepared in similar syringes for injection by the nurse who opens the drug packages (blinding nurse). Another nurse who injects the drug will remain blind throughout the study. Thus, the process by which the drug will be prepared, make it impossible to identify the

brand of Denosumab 120 mg for the patients and investigators.

Placebo
Not used

Assignment
Parallel

Other design features

Secondary Ids

empty

Ethics committees

1

Ethics committee

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Iran University of Medical Sciences

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Approval date
2020-06-22, 1399/04/02

Ethics committee reference number
IR.IUMS.REC.1399.320

2

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Approval date
2020-12-03, 1399/09/13

Ethics committee reference number
IR.SBMU.CRC.REC.1399.025

Health conditions studied

1

Description of health condition studied
Breast cancer

ICD-10 code
C50.919

ICD-10 code description
Malignant neoplasm of unspecified site of unspecified female breast

Primary outcomes

1

Description
Time to first on-study Skeletal-Related Event (SRE)

Timepoint
During a 21 months period (with monthly physician visits and imaging every 3 months)

Method of measurement
The time from the date of randomization to first SRE including date of pathologic fracture, radiation or surgery to bone, or spinal cord compression

Secondary outcomes

1

Description
Time to first and subsequent (multiple) Skeletal Related Event (SRE)

Timepoint
During a 21-month period (with monthly physician visits and imaging every 3 months)

Method of measurement
The time from the date of randomization to first and subsequent SRE

2

Description
Safety Outcomes

Timepoint
During a 21-month period

Method of measurement
Safety will be assessed based on clinical examinations and laboratory test results.

3

Description
Immunogenicity

Timepoint
Weeks 0, 24, 52, 84

Method of measurement
Blood test and antidrug antibody (ADA) presence evaluation

Intervention groups

1

Description
Denosumab (produced by AryoGen Pharmed Co.), Subcutaneous, 120 mg once every 4 weeks for 80 weeks (21 doses)

Category
Treatment - Drugs

2

Description
Xgeva®(produced by Amgen Co.), Subcutaneous, 120 mg once every 4 weeks for 80 weeks (21 doses)

Category
Treatment - Drugs

Recruitment centers

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Sponsors / Funding sources

1

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Grant name

Grant code / Reference number

Is the source of funding the same sponsor organization/entity?
Yes

Title of funding source
AryoGen Pharmed Co.

Proportion provided by this source
100

Public or private sector
Private

Domestic or foreign origin
Domestic

Category of foreign source of funding
empty

Country of origin

Type of organization providing the funding
Other

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Person responsible for updating data

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Sharing plan

Deidentified Individual Participant Data Set (IPD)
Undecided - It is not yet known if there will be a plan to make this available

Study Protocol
Undecided - It is not yet known if there will be a plan to make this available

Statistical Analysis Plan
Undecided - It is not yet known if there will be a plan to make this available

Informed Consent Form
Undecided - It is not yet known if there will be a plan to

make this available

Clinical Study Report

Undecided - It is not yet known if there will be a plan to make this available

Analytic Code

Undecided - It is not yet known if there will be a plan to make this available

Data Dictionary

Undecided - It is not yet known if there will be a plan to make this available