

# 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)  $\leq 2$ , 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 dysfunction 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

##### Name

Nassim Anjidani

##### Name of organization / entity

Orchid Pharmed

##### Country

Iran (Islamic Republic of)

##### Phone

+98 21 4347 3000

##### Email address

amini@orchidpharmed.com

**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  $\geq 2.0$  mmol/L [ $\geq 8.0$  mg/dL] and  $\leq 2.9$  mmol/L [ $\leq 11.5$  mg/dL], Serum aspartate aminotransferase (AST)  $\leq 2.5$  ULN, Serum alanine aminotransferase (ALT)  $\leq 2.5$  ULN, Serum total bilirubin  $\leq 2$  ULN, Creatinine clearance  $\geq 30$  mL/min (stage 1-3 CKD patients), Serum Creatinine  $\leq 1.5$  ULN, Leukocytes  $> 3,000$ /mcL (without growth factor), Platelets  $> 100,000$ /mcL, Hemoglobin  $\geq 8$  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 dysfunction 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****Name of ethics committee**

Iran University of Medical Sciences

**Street address**

Iran University of Medical Sciences, Shahid Hemmat Highway, Tehran

**City**

Tehran

**Province**

Tehran

**Postal code**

1415935153

**Approval date**

2020-06-22, 1399/04/02

**Ethics committee reference number**

IR.IUMS.REC.1399.320

**2****Ethics committee****Name of ethics committee**

Shahid Beheshti University of Medical Sciences

**Street address**

Shahid Beheshti University, Daneshjou Boulevard, Tehran, Tehran Province

**City**

Tehran

**Province**

Tehran

**Postal code**

1983969411

**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

### 1

#### Recruitment center

##### Name of recruitment center

Shohadaye Haft-e Tir Hospital

##### Full name of responsible person

Dr. Pedram Fadavi, Dr. Maryam Grossi, Dr. Mastane Sanei

##### Street address

Haft-e- Tir Hospital, Shahid Rajaei St., Shahr-e-rey, Tehran

##### City

Shahr-e-rey

##### Province

Tehran

##### Postal code

1886719176

##### Phone

+98 21 5522 8581

##### Email

Fadavi.p@iums.ac.ir

### 2

#### Recruitment center

##### Name of recruitment center

Omid Hospital

##### Full name of responsible person

Dr. Omid Asnaashari

##### Street address

Omid Hospital, Farhangian Blvd., Bahonar Blvd., Urmia

##### City

Urmia

##### Province

West Azarbaijan

##### Postal code

5716835344

##### Phone

+98 44 3557 1209

##### Email

omidesnaashari@gmail.com

### 3

#### Recruitment center

##### Name of recruitment center

Gilan Radiotherapy and Oncology Clinic

##### Full name of responsible person

Dr. Hamid Saeidi Saedi

##### Street address

Iran, Gilan, Rasht, Golsar, Golbagh Namaz, Gilan Radiotherapy and Oncology Clinic.

##### City

Rasht

##### Province

Guilan

##### Postal code

4144895596

##### Phone

+98 13 3375 9662

##### Email

H.Saeedi@tilburguniversity.edu

### 4

#### Recruitment center

##### Name of recruitment center

Faraz Health Clinic

##### Full name of responsible person

Dr. Fateme Homaei

##### Street address

Faraz Health Clinic, Alandasht Sq., kooch sangi St., Mashhad

##### City

Mashhad

##### Province

Razavi Khorasan

##### Postal code

1234567899

##### Phone

+98 51 3840 9183

##### Email

fatemeh\_homaei@yahoo.com

### 5

#### Recruitment center

##### Name of recruitment center

Dr. Raham Salek's office

##### Full name of responsible person

Dr. Roham Salek

##### Street address

Iran, Mashhad, East Golestan St., Opadana Building, 4th floor

##### City

Mashhad

##### Province

Razavi Khorasan

##### Postal code

9137744797

##### Phone

+98 51 3228 0676

##### Email

salekr@mums.ac.ir

### 6

#### Recruitment center

##### Name of recruitment center

Reza Radiotherapy & Oncology Center

##### Full name of responsible person

Dr. Fatemeh Varshoei Tabrizi

##### Street address

Reza Radiotherapy and Oncology Center,19 Rafsanjani St., Haftom Azar Sq., Rafsanjani Hwy.,

International Fair Blvd., Mashhad

**City**

Mashhad

**Province**

Razavi Khorasan

**Postal code**

9184166552

**Phone**

+98 51 3500 8530

**Email**

varshoef@mums.ac.ir

**7**

**Recruitment center**

**Name of recruitment center**

Imam Reza clinic

**Full name of responsible person**

Dr. Niloofar Ahmadloo

**Street address**

Iran, Shiraz, Namazi Square, next to Blood Transfusion, Imam Reza (AS) Specialized and Subspecialized Clinic

**City**

Shiraz

**Province**

Fars

**Postal code**

7193613311

**Phone**

+98 71 3212 7001

**Email**

ahmadloo@sums.ac.ir

**8**

**Recruitment center**

**Name of recruitment center**

Seyed-Al-shohada Hospital

**Full name of responsible person**

Dr. Ali Akhavan, Dr. Nadia Najafizadeh

**Street address**

Seyed-Al- shohada Hospital, Farshadi Alley, Khayam St., Isfahan

**City**

Isfahan

**Province**

Isfahan

**Postal code**

1234567899

**Phone**

+98 31 3236 8005

**Email**

ali52akhavan@yahoo.com

**9**

**Recruitment center**

**Name of recruitment center**

Golestan Hospital

**Full name of responsible person**

Dr. Hojatallah Shahbazian, Dr. Samira Razaghi, Dr. Seyed Mohammad Hosseini

**Street address**

Golestan Hospital, Farvardin St., Golestan Alley, Ahvaz

**City**

Ahvaz

**Province**

Khuzestan

**Postal code**

6136984436

**Phone**

+98 61 3374 3001

**Email**

samira\_razzaghi@yahoo.com

**10**

**Recruitment center**

**Name of recruitment center**

Imam Hussein Hospital

**Full name of responsible person**

Dr. Robab Anbiaee

**Street address**

Imam Hussein Hospital, Madani St., Tehran

**City**

Tehran

**Province**

Tehran

**Postal code**

1617763141

**Phone**

+98 21 7343 3000

**Email**

Anbiaee@gmail

**11**

**Recruitment center**

**Name of recruitment center**

Shohadaye Tajrish Hospital

**Full name of responsible person**

Dr. Mona Malekzadeh Mughani

**Street address**

Shohadaye Tajrish Hospital, Tajrish Sq., Tehran

**City**

Tehran

**Province**

Tehran

**Postal code**

1989934148

**Phone**

+98 21 2274 9201

**Email**

m.malekzade20@gmail.com

**12**

**Recruitment center**

**Name of recruitment center**

Mahdieh Clinic

**Full name of responsible person**

Dr. Negin Farshchian

**Street address**

Mahdieh Clinic, Moayed St., Kermanshah

**City**  
Kermanshah  
**Province**  
Kermanshah  
**Postal code**  
6713743640  
**Phone**  
+98 83 3727 7700  
**Email**  
farshchian.n@KUMS.ac.ir

### 13

#### **Recruitment center**

**Name of recruitment center**  
Sadra clinic  
**Full name of responsible person**  
Dr. Fatemeh Zahedi  
**Street address**  
Sadra clinic , Farjad building, No 19, No 10 Alley, 19th DEY St., Qom  
**City**  
Qom  
**Province**  
Ghoum  
**Postal code**  
3713615757  
**Phone**  
+98 25 3775 0582  
**Email**  
fzahedi58@yahoo.com

### 14

#### **Recruitment center**

**Name of recruitment center**  
Mahdieh Hospital  
**Full name of responsible person**  
Dr. Masoumeh Keshvari, Dr. Behnaz Behzadi  
**Street address**  
Mahdieh Hospital, Fadaeiyan Eslam St, Shoush Sq., Tehran  
**City**  
Tehran  
**Province**  
Tehran  
**Postal code**  
1185817511  
**Phone**  
+98 21 5506 2628  
**Email**  
masoumehkeshvari@yahoo.com

### 15

#### **Recruitment center**

**Name of recruitment center**  
Shahid Ramzanzadeh Radiotherapy Center  
**Full name of responsible person**  
Mohammad Ali Broomand  
**Street address**  
Iran, Yazd, Shahid Motahari St., in front of Rouhanioon gas station.

**City**  
Yazd  
**Province**  
Yazd  
**Postal code**  
7251174  
**Phone**  
+98 35 3725 1174  
**Email**  
mohammadalibroomand@gmail.com

### 16

#### **Recruitment center**

**Name of recruitment center**  
Ebn Sina Clinic  
**Full name of responsible person**  
Dr. Arash Parvizi  
**Street address**  
Iran, Alborz, Beheshti Street, Negin Alborz Tower  
**City**  
Karaj  
**Province**  
Alborz  
**Postal code**  
3144816877  
**Phone**  
+98 26 3447 5469  
**Email**  
parviziarash@gmail.com

### 17

#### **Recruitment center**

**Name of recruitment center**  
Omid Tehran Clinic  
**Full name of responsible person**  
Dr. Hossein Fodazi, Dr. Shiva Moghadam  
**Street address**  
Iran, Tehran, South Chamran highway, not reaching Baqer Khan, Tehran's Omid Clinic  
**City**  
Tehran  
**Province**  
Tehran  
**Postal code**  
1441763483  
**Phone**  
+98 21 6656 3216  
**Email**  
moghadamshiva@yahoo.com  
**Web page address**

## **Sponsors / Funding sources**

### 1

#### **Sponsor**

**Name of organization / entity**  
AryoGen Pharmed Co.  
**Full name of responsible person**  
Nassim Anjidani

**Street address**

Cross Tajbakhsh Street, 24th Kilometer Makhsous.

**City**

Garm Darreh

**Province**

Alborz

**Postal code**

56145226

**Phone**

+98 26 3610 6480

**Email**

contact@aryogen.com

**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

**Person responsible for general inquiries****Contact****Name of organization / entity**

Orchid Pharmed Co.

**Full name of responsible person**

Nassim Anjidani

**Position**

Medical Department Manager

**Latest degree**

Medical doctor

**Other areas of specialty/work**

Medical Pharmacy

**Street address**

No 42, Attar St., Vanak Sq.

**City**

Tehran

**Province**

Tehran

**Postal code**

1994766411

**Phone**

+98 21 4347 3000

**Email**

anjidani.n@orchipharmed.com

**Person responsible for scientific inquiries****Contact****Name of organization / entity**

Iran University of Medical Sciences

**Full name of responsible person**

Pedram Fadavi

**Position**

Assistant Professor

**Latest degree**

Ph.D.

**Other areas of specialty/work**

Radiotherapy

**Street address**

Iran University of Medical Sciences, Shahid Hemmat Highway, Tehran

**City**

Tehran

**Province**

Tehran

**Postal code**

1415935153

**Phone**

+98 21 86701

**Email**

Fadavi.p@iums.ac.ir

**Person responsible for updating data****Contact****Name of organization / entity**

Orchid Pharmed Co.

**Full name of responsible person**

Nassim Anjidani

**Position**

Medical Department Manager

**Latest degree**

Medical doctor

**Other areas of specialty/work**

Medical Pharmacy

**Street address**

No 42, Attar Neyshaboori St., Vanak Sq.

**City**

Tehran

**Province**

Tehran

**Postal code**

1994766411

**Phone**

+98 21 4347 3000

**Email**

anjidani.n@orchidpharmed.com

**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