A Randomized, Double-Blind, Multicenter Study of Denosumab Compared With Zoledronic Acid (Zometa®) in the Treatment of Bone Metastases in Subjects with Advanced Breast Cancer

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To determine if denosumab is non-inferior to zoledronic acid (Zometa) with respect to the first on-study occurrence of a skeletal-related event (SRE) in subjects with advanced breast cancer and bone metastases.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bone disorders (excl congenital and fractures)
Study type	Interventional

Summary

ID

NL-OMON31822

Source
ToetsingOnline

Brief title
Denosumab 20050136

Condition

- Bone disorders (excl congenital and fractures)
- Skeletal neoplasms malignant and unspecified

Synonym
Bone metastases in advanced breast cancer. Breast cancer spread to bone.

Research involving
Human

Sponsors and support

Primary sponsor: AMGEN Inc.
Source(s) of monetary or material Support: Sponsor: Amgen Inc.;Thousand Oaks;California;U.S.A.

Intervention

Keyword: Bone metastases, Breast cancer, Denosumab, Zoledronic Acid

Outcome measures

Primary outcome

Time to the first on-study SRE (non-inferiority)

Secondary outcome

Secondary Efficacy Endpoints

* time to the first on-study SRE (superiority)

* time to the first-and-subsequent on-study SRE (superiority, using multiple

event analysis)

Safety Endpoints

* subject incidence of treatment-emergent adverse events

* changes in laboratory values

* Incidence of anti-denosumab antibody (binding and neutralizing) formation

Study description

Background summary

Worldwide, there were approximately 1,150,000 cases of breast cancer reported in 2002 with 411,000 deaths. 75% of metastatic breast cancer patients will develop bone metastases. Over 50% of all breast cancer patients with bone metastases exhibit pathologic fractures. Besides systemic antineoplastic treatment, radiation therapy to bone has been the mainstay of controlling metastatic bone disease. Other widely used palliative treatments of metastatic

bone disease are bisphosphonates, which have been shown to reduce the incidence of SREs, bone pain, and hypercalcemia in patients with bone metastasis in several randomized clinical trials. While they have proven to be good inhibitors of bone resorption, it has become clear that their anti-resorptive activity resides in their ability to inhibit osteoclast activities, rather than their physicochemical properties. There is previous clinical experience with Denosumab in the treatment of prevention osteoporosis, and cancer associated bone diseases.

Study objective

To determine if denosumab is non-inferior to zoledronic acid (Zometa) with respect to the first on-study occurrence of a skeletal-related event (SRE) in subjects with advanced breast cancer and bone metastases.

Study design

Approximately 1690 subjects will be randomized in a 1:1 ratio to receive either denosumab, administered at a dose of 120 mg subcutaneously (SC) every 4 weeks (Q4W), or zoledronic acid administered intravenously (IV) at a dose of 4 mg (equivalent creatinine clearance-adjusted dose in subjects with baseline creatinine clearance <= 60 ml/min) as a single, minimum 15-minute infusion Q4W in a blinded manner. Each subject will receive either an SC injection of denosumab and an IV infusion of zoledronic acid placebo Q4W, or an SC injection of denosumab placebo and an IV infusion of zoledronic acid Q4W until approximately 745 subjects have experienced at least one on-study SRE and the primary efficacy and safety analysis is completed. SRE is defined as pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression.
It is strongly recommended that all subjects receive daily supplements of at least 500 mg calcium and at least 400 IU of vitamin D, unless documented hypercalcemia.

If Denosumab is determined to have an positive benefit:risk profile compared with zoledronic acid, all subjects currently undergoing every 4 weeks scheduled assessments will be offered open-label denosumab at a dose of 120 mg SC until subjects have access to commercially available product or for up to 2 years, which ever comes first. If benfit:risk profile is not positive, all subjects will be followed for survival for 2 years after the last dose of blinded IP.

Intervention

IV injections (Zometa or placebo): every 4 weeks, SC injections: Denosumab or placebo: every 4 weeks, Totally skeletal X-rays: every 12 weeks, Blood sampling at screening and every 4 weeks. See also protocol version 30 April 2008 p. 80-82.

Open-label phase: SC injections Denosumab every 4 weeks, Blood sampling every 4 weeks during the first 3 months, subsequently every 12 weeks. See also protocol version 30 April 2008 p. 83.

Study burden and risks

There could be allergic reactions to the s.c injections and iv administering of the medication.
The blood sampling can cause bruising and pain.

Known adverse events of Denosumab are temporary decrease in blood calcium levels with symptoms of tingling sensation or muscle cramping.
Fatique, muscle stiffness, weakness, bone pain constipation, upper respiratory inflammation or pain, diarrhea, abnormal touch sensation or itching or redness of the skin.
Infrequently development of antibodies to denosumab has occured.

Zoledronic acid: Adverse events reported by patients using intravenous bisphosphonates include (but are not limited to) the following: fever, nausea, constipation, diarrhea, vomiting, abdominal pain, bone and muscle pain, anemia (low red blood cell counts), fatigue, cough, difficulty breathing, weakness, and swelling of lower limbs.
Damage to the jaw bone (also called osteonecrosis of the jaw or ONJ) has been reported in patients with cancer receiving treatment regimens that include bisphosphonates.

The benefit for subjects is that all will be treated by an active drug shown to be effective in regards to delaying or preventing SRE occurance .

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Inclusion Criteria:
* adult (men included) with histologically or cytologically confirmed breast adenocarcinoma
* current or prior radiographic (ie, x-ray, computer tomography [CT], or magnetic resonance imaging [MRI]) evidence of at least 1 bone metastasis
* Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2
* adequate organ function as defined by the following criteria:
* serum aspartate aminotransferase (AST) less than or equal to 5 x upper limit of normal (ULN)
* serum alanine aminotransferase (ALT) less than or equal to 5 x ULN
* serum total bilirubin less than or equal to 2 x ULN
* creatinine clearance (Cockcroft-Gault) equal or higher to 30 mL/min
* albumin-adjusted serum calcium equal or higher to 2.0 mmol/L (8.0 mg/dL) and less than or equal to 2.9 mmol/L (11.5 mg/dL)
* Before any study-specific procedure is performed, the appropriate written informed consent must be obtained.

Exclusion criteria

Exclusion Criteria:
* current or prior IV bisphosphonate administration
* current or prior oral bisphosphonate for the treatment of bone metastasis
* planned radiation therapy or surgery to bone
* prior administration of denosumab
* known brain metastases
* life expectancy less than 6 months
* prior history or current evidence of osteonecrosis/osteomyelitis of the jaw
* active dental or jaw condition that requires oral surgery

* non-healed dental/oral surgery
* planned invasive dental procedure over the course of the study
* evidence of any of the following conditions per subject self report or medical chart review:
* any prior malignancy (other than breast cancer, basal cell carcinoma or in situ cervical cancer) with active disease within 3 years before randomization
* known infection with human immunodeficiency virus
* active infection with Hepatitis B virus or Hepatitis C virus
* any organic or psychiatric disorder that, in the opinion of the investigator, might prevent the subject from completing the study or interfere with the interpretation of the study results
* thirty days or less since receiving an investigational product or device (ie, does not have marketing authorization) in another clinical trial
* subject with reproductive potential who will not agree to use effective contraception (as defined by the principal investigator or designee)
* known sensitivity to any of the products to be administered during the study (eg, zoledronic acid, mammalian derived products, calcium or vitamin D)

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-01-2007
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	nvt
Generic name:	denosumab
Product type:	Medicine
Brand name:	Zoledronic Acid
Generic name:	Zoledronic Acid
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	04-05-2006
Application type:	First submission
Review commission:	METC Zuidwest Holland (Den Haag)
Approved WMO Date:	26-06-2006
Application type:	First submission
Review commission:	METC Zuidwest Holland (Den Haag)
Approved WMO Date:	02-08-2006
Application type:	Amendment
Review commission:	METC Zuidwest Holland (Den Haag)
Approved WMO Date:	20-10-2006
Application type:	Amendment
Review commission:	METC Zuidwest Holland (Den Haag)
Approved WMO Date:	09-01-2007
Application type:	Amendment
Review commission:	METC Zuidwest Holland (Den Haag)
Approved WMO Date:	21-05-2007
Application type:	Amendment
Review commission:	METC Zuidwest Holland (Den Haag)
Approved WMO Date:	06-08-2007

Application type:	Amendment
Review commission:	METC Zuidwest Holland (Den Haag)
Approved WMO Date:	18-09-2007
Application type:	Amendment
Review commission:	METC Zuidwest Holland (Den Haag)
Approved WMO Date:	05-10-2007
Application type:	Amendment
Review commission:	METC Zuidwest Holland (Den Haag)
Approved WMO Date:	22-01-2008
Application type:	Amendment
Review commission:	METC Zuidwest Holland (Den Haag)
Approved WMO Date:	28-02-2008
Application type:	Amendment
Review commission:	METC Zuidwest Holland (Den Haag)
Approved WMO Date:	21-05-2008
Application type:	Amendment
Review commission:	METC Zuidwest Holland (Den Haag)
Approved WMO Date:	08-07-2008
Application type:	Amendment
Review commission:	METC Zuidwest Holland (Den Haag)
Approved WMO Date:	12-05-2009
Application type:	Amendment
Review commission:	METC Zuidwest Holland (Den Haag)
Approved WMO Date:	11-08-2009
Application type:	Amendment
Review commission:	METC Zuidwest Holland (Den Haag)
Approved WMO Date:	06-10-2009

Application type:	Amendment
Review commission:	METC Zuidwest Holland (Den Haag)
Approved WMO Date:	25-03-2010
Application type:	Amendment
Review commission:	METC Zuidwest Holland (Den Haag)
Approved WMO Date:	15-06-2010
Application type:	Amendment
Review commission:	METC Zuidwest Holland (Den Haag)
Approved WMO Date:	20-09-2010
Application type:	Amendment
Review commission:	METC Zuidwest Holland (Den Haag)
Approved WMO Date:	14-01-2011
Application type:	Amendment
Review commission:	METC Zuidwest Holland (Den Haag)
Approved WMO Date:	14-07-2011
Application type:	Amendment
Review commission:	METC Zuidwest Holland (Den Haag)
Approved WMO Date:	29-08-2011
Application type:	Amendment
Review commission:	METC Zuidwest Holland (Den Haag)
Approved WMO Date:	25-10-2011
Application type:	Amendment
Review commission:	METC Zuidwest Holland (Den Haag)
Approved WMO Date:	09-11-2011
Application type:	Amendment
Review commission:	METC Zuidwest Holland (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2006-000339-93-NL
CCMO	NL11609.098.06