A phase 1 double blind, placebo controlled study of ALX-0141 single dose subcutaneous administration in healthy post-menopausal women

Published: 18-11-2009
Last updated: 04-05-2024

- to determine the maximum tolerated dose (MTD) and/or biological effective dose (BED) after single s.c. administration of ALX-0141 - to determine the safety and tolerability of escalating single doses of ALX-0141 in healthy postmenopausal women

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

Summary

ID

NL-OMON32748

Source
ToetsingOnline

Brief title
ALX-0141 s.c. SAD study

Condition

- Bone disorders (excl congenital and fractures)

Synonym
Bone loss

Research involving
Human

Sponsors and support

Primary sponsor: Ablynx N.V.

Source(s) of monetary or material Support: Farmaceutische Industrie.

Intervention

Keyword: ALX-0141, Healthy Post-Menopausal women, Osteoporosis

Outcome measures

Primary outcome

Pharmacodynamics:

P1NP, CTX-1, BAP and TRACP5b concentrations in serum and creatinin, CTX-1& and

NTX 1 concentrations in urine.

Pharmacokinetics:

Plasma ALX-0141 concentrations, pharmacokinetic parameters.

Safety:

AEs, local tolerability, vital signs, 12-lead ECG, clinical laboratory,

physical examination, immunogenicity, 25-hydroxy vitamin D in serum,

immunophenotyping of WBC.

Secondary outcome

NA

Study description

Background summary

The drug to be given, ALX-0141, is a new, investigational compound that may eventually be used for the treatment of bone loss.
The skeletal system is constantly remodeling in response to hormonal and gravitational signals from the environment. This continuous remodeling consists

of two linked processes: bone resorption (loss of bone substance) and bone formation. Both processes are in balance in a healthy body. ALX-0141 is expected to help restore balance between bone resorption and bone formation in certain diseases like osteoporosis or rheumatoid arthritis. ALX-0141 is a so-called nanobody which means that it is a very small simple protein that is a fraction of an antibody binding to receptors on cells that are involved with bone resorption and bone formation. Some of the advantages of these fragmented antibodies in comparison to normal antibodies (monoclonal antibodies) are that they are produced more easily and they are less likely to cause any allergic reactions.

Study objective

- to determine the maximum tolerated dose (MTD) and/or biological effective dose (BED) after single s.c. administration of ALX-0141
- to determine the safety and tolerability of escalating single doses of ALX-0141 in healthy postmenopausal women

Study design

Design:
A double-blind, placebo controlled, single-ascending dose study in 1 cohort of 2 healthy postmenopausal female subjects receiving a single subcutaneous (s.c.) dose of ALX-0141 or placebo (1 verum and 1 placebo) and 5 cohorts of 8 healthy postmenopausal female subjects receiving a single s.c. dose of ALX-0141 or placebo (6 verum and 2 placebo).

Procedures and assessments
Screening and each follow-up visit:
Clinical laboratory (including Ca and intact-parathyroid hormone (PTH)), 25 hydroxy vitamin D in serum, immunophenotyping of white blood cells (WBC) vital signs, physical examination (at screening and first follow-up visit only), weight, 12-lead ECG (in triplicate at screening), immunogenicity, pharmacokinetics (PK), pharmacodynamics (PD);
At eligibility screening: medical history, height, mammogram#, drug and alcohol screen, HBsAg, anti HCV and anti HIV 1/2; clinical laboratory (including Ca and intact-PTH), 25 hydroxy vitamin D, immunophenotyping of WBC, weight, drug and alcohol screen, vital signs and ECG to be repeated upon admission

Observation period:
One period in clinic from -65 h (Day -3) before up to 144 h after drug administration on Day 1 and ambulatory visits on Day 14±2, 30±2, 60±5 and 90±5 (follow-up) and additional follow-up visits if necessary*.

Blood sampling:
For PK of ALX-0141 in plasma: pre-dose and 8 h and 12 h post-dose, once in the

morning on Days 2-7 and once on Days 14±2, 30±2, 60±5 and 90±5 (follow-up) and additional follow-up visits if necessary*.
For PD of procollagen type I amino-terminal propeptide (P1NP), cross-linking telopeptide of type 1 collagen (CTX-1), bone specific alkaline phosphatase (BAP) and tartrate resistant acid phosphatase (TRACP5b) in serum: at screening, once in the mornings on Days -2, -1, pre dose and 8 h and 12 h post-dose on Day 1, and once in the morning on Days 2, 3, 4, 5, 6, 7, 14±2, 30±2, 60±5 and 90±5 (follow-up) and additional follow-up visits if necessary*. Samples should be taken at the same timepoints.
For immunogenicity (anti-drug antibodies in plasma): once on Days -2, -1, 1 (pre-dose), 7, 14±2, 30±2, 60±5 and 90±5 (follow-up) and additional follow-up visits if necessary*.
For additional study related research on immunogenicity: once on Day -2 and Day 60±5.

Urine sampling:
For PD of CTX-1& and N-terminal telopeptide of type 1 collagen (NTX-1), creatinin (under fasted conditions) in urine: at screening, once on Days 2, -1, 1 (pre-dose), 2, 3, 4, 5, 6, 7, 14±2, 30±2, 60±5 and 90±5 (follow-up) and additional follow-up visits if necessary*.

Safety assessments:
Adverse events (AEs) and local tolerability: throughout the study; vital signs and 12-lead electrocardiogram (ECG): pre-dose (ECG in triplicate) and 3, 6, and 9 h post-dose on Day 1, once in the morning on Days 2-7 and once on Days 14±2, 30±2, 60±5 and 90±5 (follow-up) and additional follow-up visits if necessary*; clinical laboratory (including Ca and intact-PTH), 25-hydroxy vitamin D, immunophenotyping of WBC to differentiate between B and T lymphocytes: once on Days 1, 2, 4, 6, 14±2, 30±2, 60±5 and 90±5 (follow-up) and additional follow-up visits if necessary*; immunogenicity at pre-dose Day 1, Days 7, 14±2, 30±2, 60±5 and 90±5 (follow-up) and additional follow-up visits if necessary*.

Bioanalysis:
Analysis of plasma ALX-0141 samples using a validated method by PRA.
Analysis of serum P1NP, CTX-1, BAP and TRACP5b samples using validated methods by PRA.
Analysis of urine creatinin, NTX-1, CTX-1 (optional&) samples using validated methods by PRA.
Analysis of anti-drug antibodies (ADA) samples using validated methods by PRA.
Analysis of 25-hydroxy vitamin D using a validated method by PRA.
Immunophenotyping of WBC using validated methods by PRA.
Analysis of immunogenicity using validated methods by Ablynx NV.

only applicable if no mammogram was conducted within 9 months prior to the study
* a monthly additional follow-up visit will be conducted if CTX-1 levels are not back to baseline - 30% at Day 90 and will be repeated until CTX-1 levels

are back to baseline - 30%
& CTX-1 urine samples will be frozen and analyzed upon request of the Sponsor

Intervention

Study Medication:
Active substance : ALX-0141
Activity : anti-RANKL
Indication : bone loss
Strength : 65 mg/mL
Dosage form : s.c. injection

Treatments :
Cohort 1: a single s.c. dose of 0.003 mg/kg of ALX-0141 (n=1) or placebo (n=1) on Day 1
Cohort 2: a single s.c. dose of 0.01 mg/kg of ALX-0141 (n=6) or placebo (n=2) on Day 1
Cohort 3: a single s.c. dose of 0.03 mg/kg of ALX-0141 (n=6) or placebo (n=2) on Day 1
Cohort 4: a single s.c. dose of 0.1 mg/kg of ALX-0141 (n=6) or placebo (n=2) on Day 1
Cohort 5: a single s.c. dose of 0.3 mg/kg of ALX-0141 (n=6) or placebo (n=2) on Day 1
Cohort 6: a single s.c. dose of 1 mg/kg of ALX-0141 (n=6) or placebo (n=2) on Day 1

Study burden and risks

Procedures:
Pain, light bleeding, heamatoma, possibly an infection.

Medication:
As ALX-0141 will be administered to man for the first time in this study, adverse effects in man have not been reported to date. In previous studies with cynomolgus monkeys, in which ALX-0141 was administered in 6 high doses over a period of 2weeks, the following adverse effect was observed in one animal: clinical signs of what was thought to be the consequence of low blood calcium concentration (body tremor and muscle spasm); additionally a mild reaction on the injection site was seen that spontaneously recovered swiftly.

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

Healthy post menopausal women, 18 - 80 years old, BMI between 18 and 36 kg/m2, moderate or non-smoker.

Exclusion criteria

Suffering from: hepatitis B, cancer or HIV/AIDS. In case of participation in another drug study within 60 days before the start of this study or being a blood donor within 60 days from the start of the study. In case of donating more than 1.0 liters of blood in the 10 months prior the start of this study.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-12-2009
Enrollment:	42
Type:	Actual

Ethics review

Approved WMO

Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2009-016359-24-NL
CCMO	NL30520.056.09