**Summary**

- **Objective:** Study design and demographics
  - Healthy postmenopausal women (53-77 years, mean 68 years)
  - Randomised 1:1 to placebo or ALX-0141
  - Treatment schedule: 1 mg/kg ALX-0141 [n=6], 0.1 mg/kg ALX-0141 [n=6], 0.03 mg/kg ALX-0141 [n=6], 0.003 mg/kg ALX-0141 [n=1]

- **Pharmacokinetics (PK):**
  - Geometric mean plasma concentrations of ALX-0141
  - **IC50** values for effect on biochemical markers:
    - Serum CTX-1: 1.8 µg/ml
    - Serum P1NP: 1.8 µg/ml
  - Summary of PK parameters:
    - **Time Relative to Dosing:** Days 0, 1, 30, 60, 90, 120

- **Pharmacodynamics (PD):**
  - **Time Relative to Dosing:** Days 0, 1, 30, 60, 90, 120
  - **Concentration:** µg/ml

- **Safety and tolerability:**
  - No serious adverse events
  - Most frequent TEAEs: musculoskeletal and connective tissue

- **Conclusion:** ALX-0141 was well tolerated and showed a favourable PK profile, triggering a prolonged PD response.

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**Study design and demographics**

- **Phase I study design and treatment schedule**
  - Healthy postmenopausal women [n=42]
  - Randomised 1:1 to placebo or ALX-0141
  - Dose levels: 0.003 mg/kg ALX-0141 [n=1], randomised 1:1 to placebo

- **Objectives**
  - Determine safety and tolerability of single SC doses
  - Key inclusion criteria:
    - Healthy postmenopausal women ≥ 50 years old
    - Body mass index (BMI) ≥ 18.0 kg/m²
    - Normal lab parameters
    - No history of relevant disease
    - No use of concomitant medication

- **Other PD markers**
  - Mean tartrate-resistant acid phosphatase type 5b (TRACP5b) concentrations
  - Concentrations of osteoblast activity
  - Less bone formation as a result of the anti-RANKL effects

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**Ablynx’s Nanobodies and ALX-0141**

- **Conventional antibody**
  - High-affinity chimeric antibody for bone resorption
  - Humanized antibody
  - Fully human heavy chains and variable light chains

- **Heavy-chain antibody**
  - Human heavy chains and constant light chains

**Other PK parameters**

- **Concentration (µg/mL)**
  - Time Relative to Dosing (days)

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**Summary of TEAE by relationship and intensity**

- **Time Relative to Dosing (days)**
  - 0, 1, 30, 60, 90, 120

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**Safety and tolerability**

- **Summary of TEAE by relationship and intensity**
  - Majority were not considered related to study medication
  - Most frequent TEAEs related to bone resorption, CTX-1 decreased in all ALX-0141 treated subjects
  - Most TEAEs were transient and resolved at the time of last visit; 11 were on-going. These were considered remote or not-related.

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**Other PD markers**

- **Mean tartrate-resistant acid phosphatase type 5b (TRACP5b) concentration**
  - Similar profiles as for serum CTX-1 levels: rapid and dose-dependent decreases, and notable inhibition already with 0.003 mg/kg ALX-0141

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**Pharmacodynamics (PD) –CTX-1**

- **Time Relative to Dosing (days)**
  - 0, 1, 30, 60, 90, 120

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**Summary of safety data**

- **Total 42 13 9 94 27 0 0 1 1 0 0 1 1 13 9 96 27 109 30**

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**Pharmacokinetics (PK)**

- **Geometric mean plasma concentrations of ALX-0141**
  - ALX-0141 administered on Day 1 and plasma concentrations were determined at multiple time points.
  - Mean geometric data for 0.003 (0.01, 0.03) mg/kg, 0.1 (0.11, 0.19) mg/kg and 1 (0.97, 1.87) mg/kg dosing, with standard deviation.

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**Pharmacodynamics (PD) – CTX-1**

- **Time Relative to Dosing (days)**
  - 0, 1, 30, 60, 90, 120

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**Conclusions**

- **After single SC injection, ALX-0141 showed a favourable PK profile, triggering a prolonged PD response. Serum levels of the lead biomarker for bone resorption, CTX-1, decreased rapidly in all ALX-0141 treated subjects and stayed significantly suppressed (below 70% of the baseline level) up to 330 days after administration at the highest dose level.**

- **The safety analysis indicated that ALX-0141 was well tolerated. No serious adverse events or dose-limiting toxicity occurred. There were no significant differences in the frequencies and severities of adverse events for subjects receiving ALX-0141 compared with placebo-treated subjects. All treatment related adverse events were transient, of mild intensity, and did not result in any study withdrawals.**

- **The results from this Phase I trial indicate that ALX-0141 is a potent RANKL inhibitor and can be administered over a wide range of doses. This data supports the further development in bone-resorptive diseases with reduced BMD and increased fracture risk, such as in cancer-related bone diseases, osteoporosis and other disorders.**

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