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Phase 3 Study of Denosumab Biosimilar HLX14 in Postmenopausal Women at High Fracture Risk: A Randomized, Double-blind, Multicenter Trial Comparing Efficacy and Safety with Reference Denosumab

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Disclosure of Interests

- My disclosure along with my co-authors is listed on the ORS website.
- I do not have a conflict with this presentation.

Background

- Postmenopausal osteoporosis is the most common type of primary osteoporosis, a metabolic bone disorder and an established risk factor for fragility fracture that leads to serious morbidity and mortality concerns[1].
- As the average life-expectancy is likely to continue to increase, the prevalence of fractures due to osteoporosis are expected to rise, thus posing a major global health issue.
- Denosumab, an anti-RANKL monoclonal antibody, binds RANKL and prevent the activation of RANK to increase bone mineral density[2,3], and is approved and well-established therapy for reducing fracture rates in postmenopausal women with osteoporosis at high risk for fracture[4,5].

HLX14 (anti-RANKL monoclonal antibody) is a proposed denosumab biosimilar. Similarity in PK, PD, safety, and immunogenicity with reference denosumab was previously shown in phase 1 study in healthy subjects[6].

Here we report the efficacy, PD, and safety in a phase 3 study of HLX14 vs. European Union-sourced reference denosumab (EU-denosumab) in postmenopausal women with osteoporosis at high risk of fracture.

PD, pharmacodynamics; PK, pharmacokinetics; RANKL, receptor activator of nuclear factor kappa-B ligand.

1. Compston JE, McClung MR & Leslie WD. *Lancet*. **2019**;393(10169):364–376. 2. Cummings SR, *et al. N Engl J Med*. **2009**;361(8):756-765. 3. Bone HG, *et al. Lancet Diabetes Endocrinol*. **2017**;5(7):513-523. 4. PROLIA®, denosumab, Amgen Inc., Thousand Oaks, CA, 2020. 5. XGEVA®, denosumab, Amgen Inc., Thousand Oaks, CA, 2020. 6. Clin Transl Sci. 2024 Dec;17(12):e70089. doi: 10.1111/cts.70089.

Study Design

A randomized, double-blind, multicenter, phase 3 trial (NCT05352516)

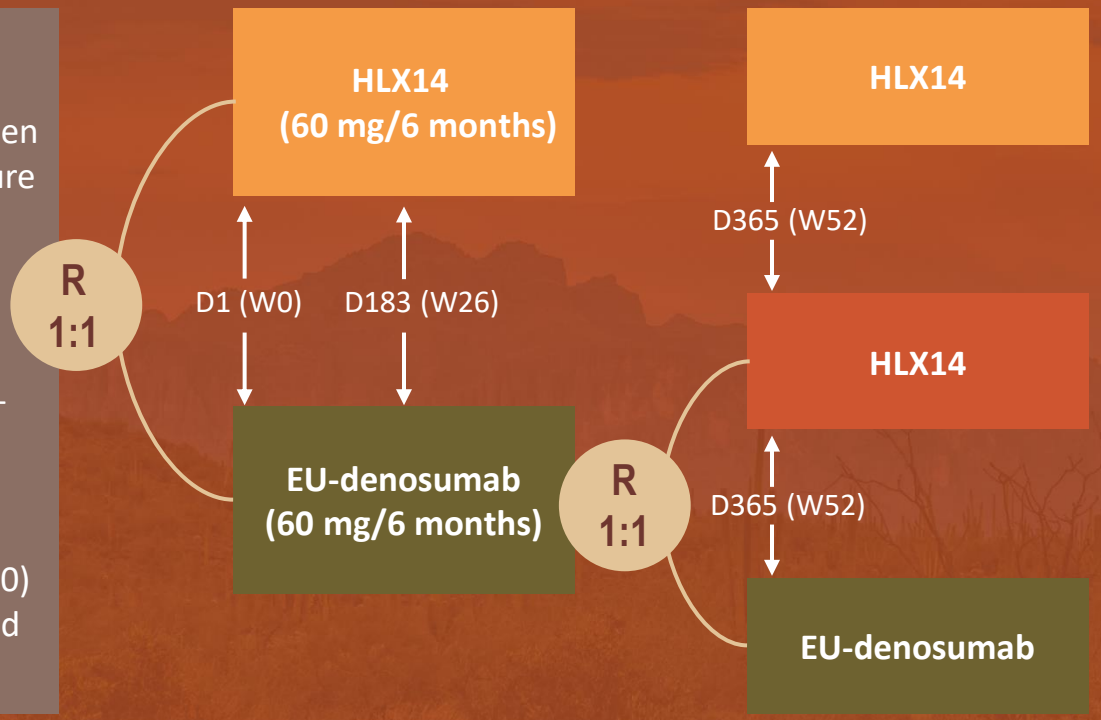
Screening (D−28 to D−1)	Treatment period 1 (W0 to W52)	Treatment period 2 (W52 to W78)

Subjects

- Osteoporosis in postmenopausal women with high risk of fracture
- Aged ≥ 60 and ≤ 90 years
- BMD T-score: −4.0 < T-score ≤ −2.5

Stratification factor

- BMI (<25, 25 to 30, >30)
- Geographics (Asian and non-Asian)



Primary endpoints

- **Efficacy: % change in BMD at lumbar spine from baseline to Week 52**
- **PD: AUEC of percent change of s-CTX from baseline to Week 26 ($AUEC_{0\text{-}26W}$)**

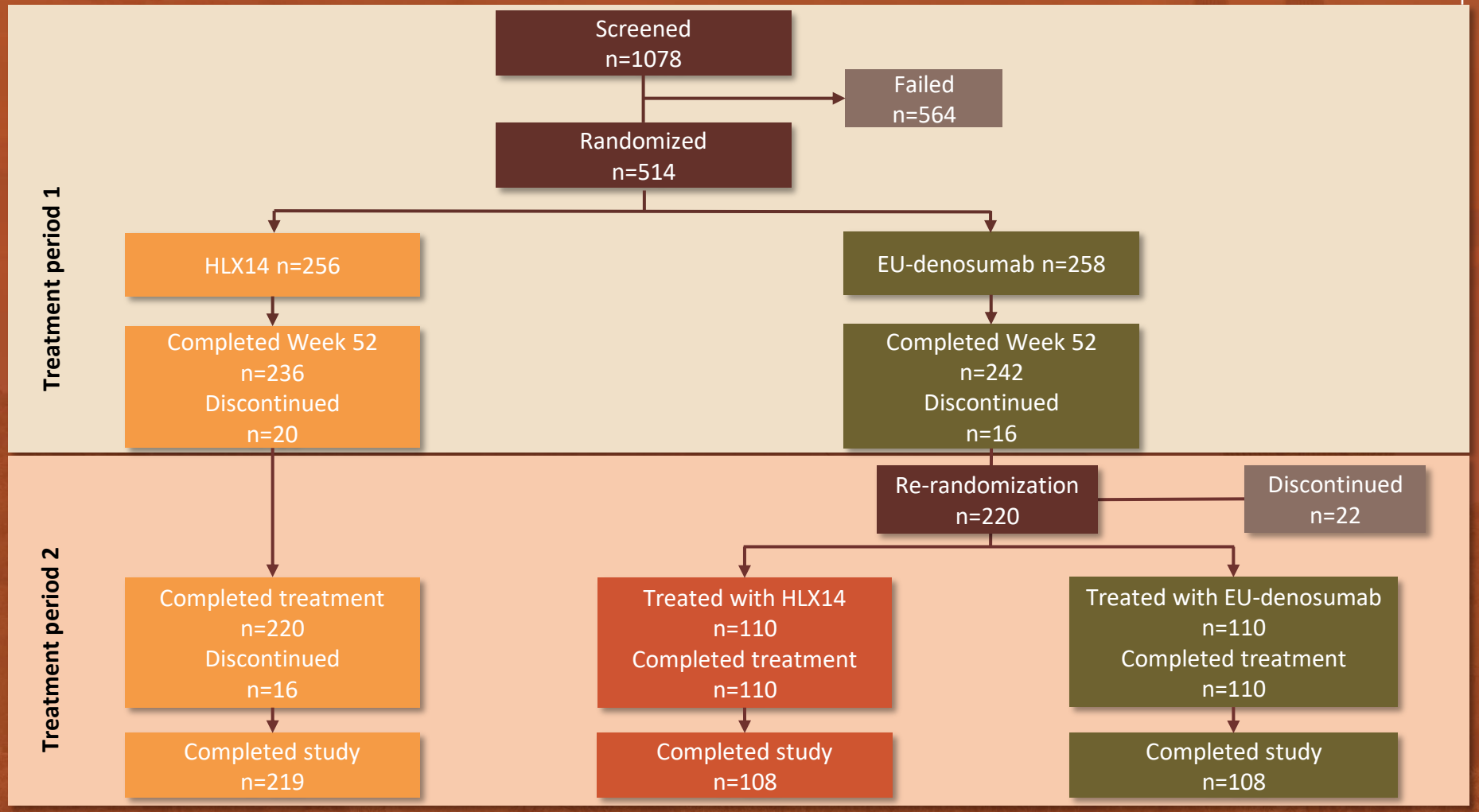
Secondary endpoints

- Rate of new fractures;
- % change from baseline in BMD at lumbar spine, total hip, femoral neck at Weeks 26 and 78 (as well as Week 52 for total hip and femoral neck);
- % change from baseline in s-CTX and s-P1NP levels;
- PK, Safety and immunogenicity

Concomitant medications: Taking at least 1000 mg of calcium, and at least 400 IU of vitamin D daily

AUEC, area under the effect-time curve; BMD, bone mineral density; BMI, body mass index; D, day; EOS, end of study; PK, pharmacokinetics; s-CTX, serum type I collagen C-telopeptide; s-P1NP, serum procollagen type 1 N telopeptide; W, week.

Subjects' Disposition



Baseline Characteristics

Characteristics	HLX14 (N = 256)	EU-denosumab (N = 258)
Age (years), median (range)	67.0 (52-87)	67.0 (51-86)
Asian, n (%)	255 (99.6)	257 (99.6)
BMI (kg/m^2), Mean (SD)	23.3 (2.9)	23.4 (3.0)
LS-BMD (g/cm2), Mean (SD)[a]	0.736 (0.079)	0.739 (0.080)
TH-BMD (g/cm2), Mean (SD)[a]	0.705 (0.092)	0.702 (0.093)
FN-BMD (g/cm2), Mean (SD)[a]	0.614 (0.101)	0.614 (0.102)
T-score at lumbar spine, Mean (SD)[a]	−3.213 (0.595)	−3.208 (0.546)
s-CTX (ng/mL), Mean (SD)	0.493 (0.221)	0.501 (0.227)
s-P1NP (ng/mL), Mean (SD)	701.849 (267.271)	683.556 (290.032)
Family history of hip fracture, n (%)	16 (6.3)	23 (8.9)
Fracture history of spine or vertebrae, n (%)	39 (15.2)	37 (14.3)
Calcium (mmol/L), Mean (SD)	2.4 (0.1)	2.4 (0.1)
25-Hydroxyvitamin D3 (nmol/L), Mean (SD)	71.4 (18.0)	71.6 (19.2)

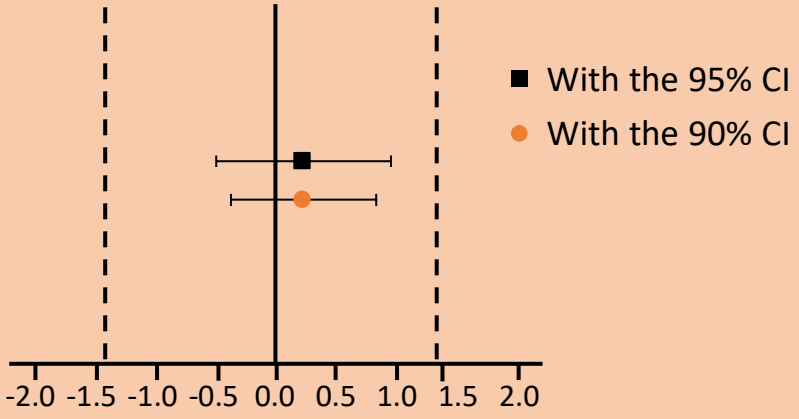
[b]Assessed by central imaging. BMI = Weight (kg) /Height (m)^2.
BMD, bone mineral density; BMI, body mass index; FN, femoral neck; LS, lumbar spine; SD, standard deviation; s-CTX, serum type I collagen C-telopeptide; s-P1NP, serum procollagen type 1 N telopeptide; TH, total hip.

Primary Efficacy and PD Endpoints

Efficacy[a], Mean (SD) for % change in LS-BMD at Week 52

Mean % change from baseline in LS-BMD (SD)	
HLX14 (N = 256)	EU-denosumab (N = 258)
6.10 (3.951)	5.90 (3.834)
Adjusted mean difference (HLX14 vs. EU-denosumab), %: 0.23 95% CI: −0.48, 0.95, p-value: 0.518 90% CI: −0.36, 0.83, p-value: 0.518	

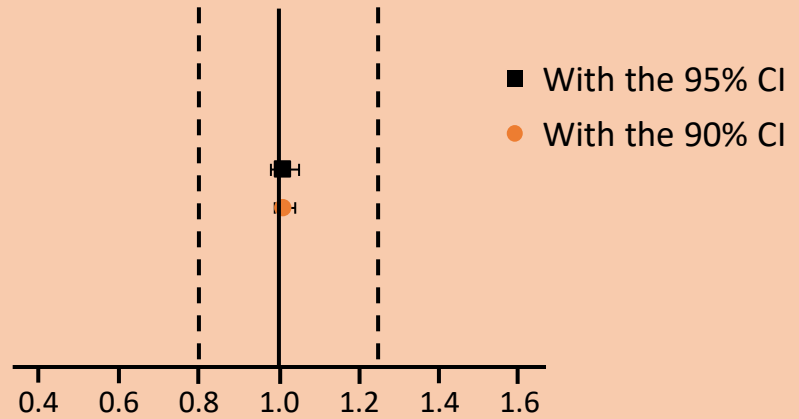
Mean difference (HLX14 vs. EU-denosumab) with the 95% and 90% CIs



PD[b], $AUEC_{0\text{-}26W}$

GeoMean (CVb%) of $AUEC_{0\text{-}26W}$	
HLX14 (N = 234)	EU-denosumab (N = 237)
14075.1253 (17.3)	13883.3613 (17.9)
GeoMean ratio (HLX14 / EU-denosumab): 1.01 95% CI: 0.98, 1.05 90% CI: 0.99, 1.04	

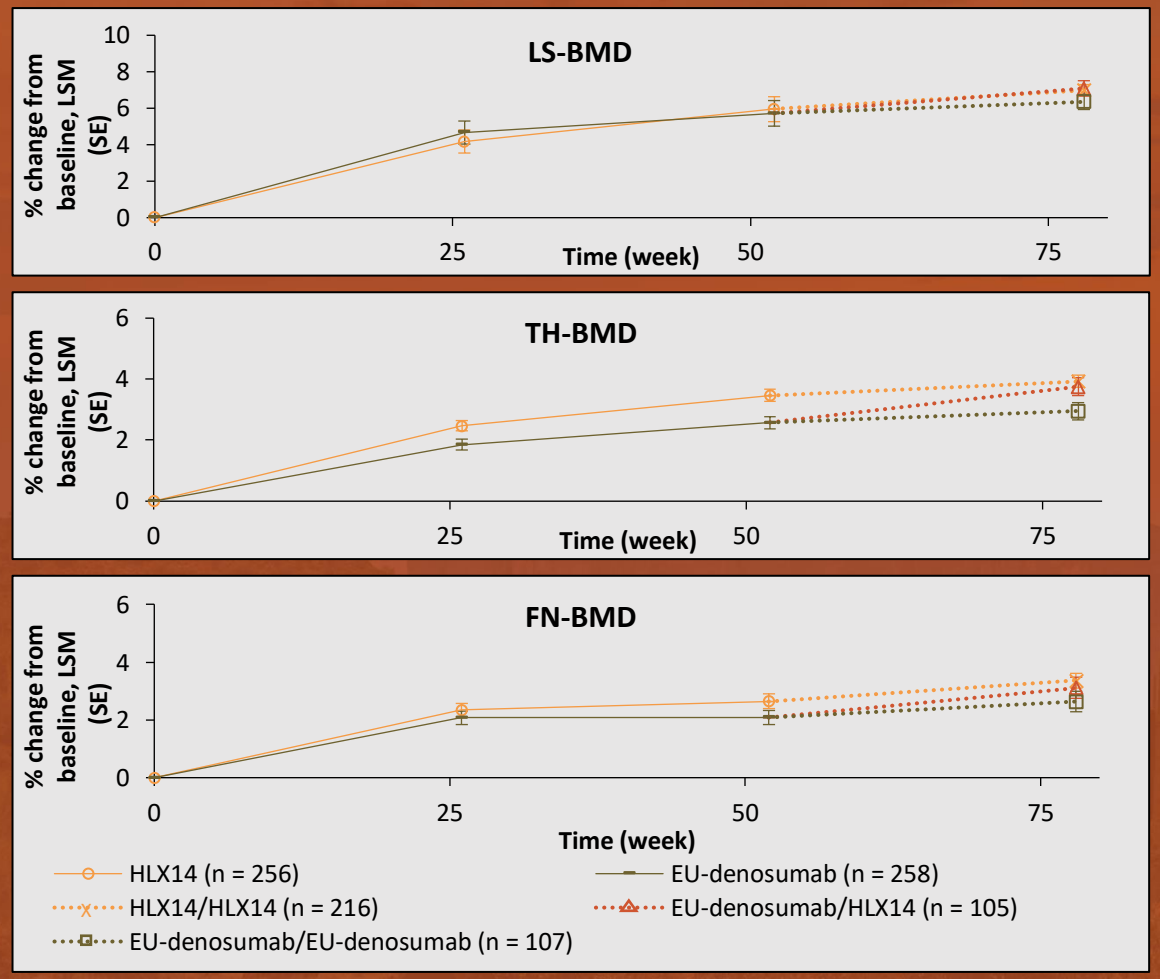
GeoMean ratio (HLX14 vs. EU-denosumab) with the 95% and 90% CIs

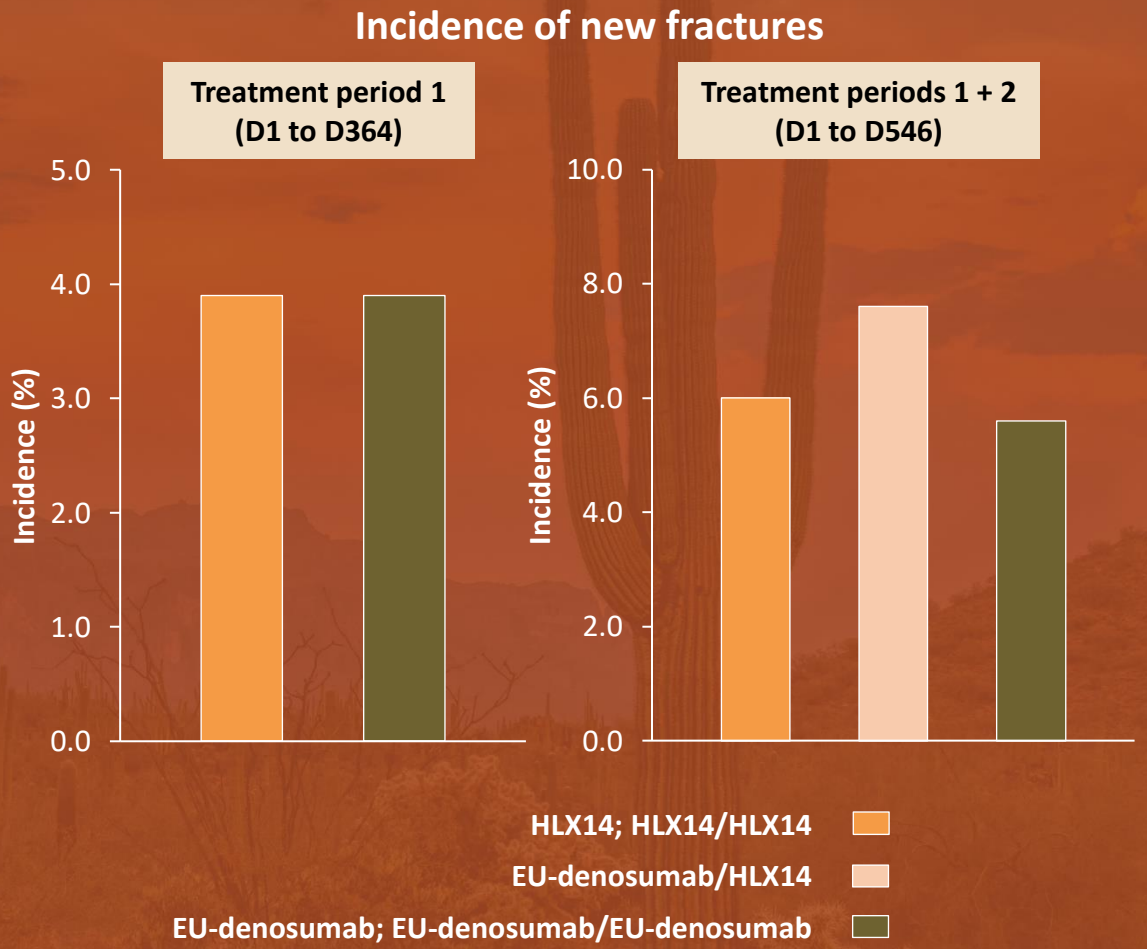


[a]Efficacy equivalence was concluded if the 90% and 95% CI of the adjusted mean difference falls within the prespecified equivalence margins of ±1.45. [b]PD equivalence was concluded if the 90% and 95% CI of the adjusted mean difference falls within the prespecified equivalence margins of 0.8 and 1.25.

$AUEC_{0\text{-}26W}$, area under the effect-time curve of percent change of s-CTX from baseline to Week 26; CI, confidence interval; CVb, geometric coefficient of variation; LS-BMD, lumbar spine bone mineral density; SD, standard deviation.

Secondary Efficacy Endpoints





CI, confidence interval; D, day; FN-BMD, femoral neck bone mineral density; LS-BMD, lumbar spine bone mineral density; LSM, least square mean; SE, standard error; TH-BMD, total hip bone mineral density.

Secondary PD Endpoints

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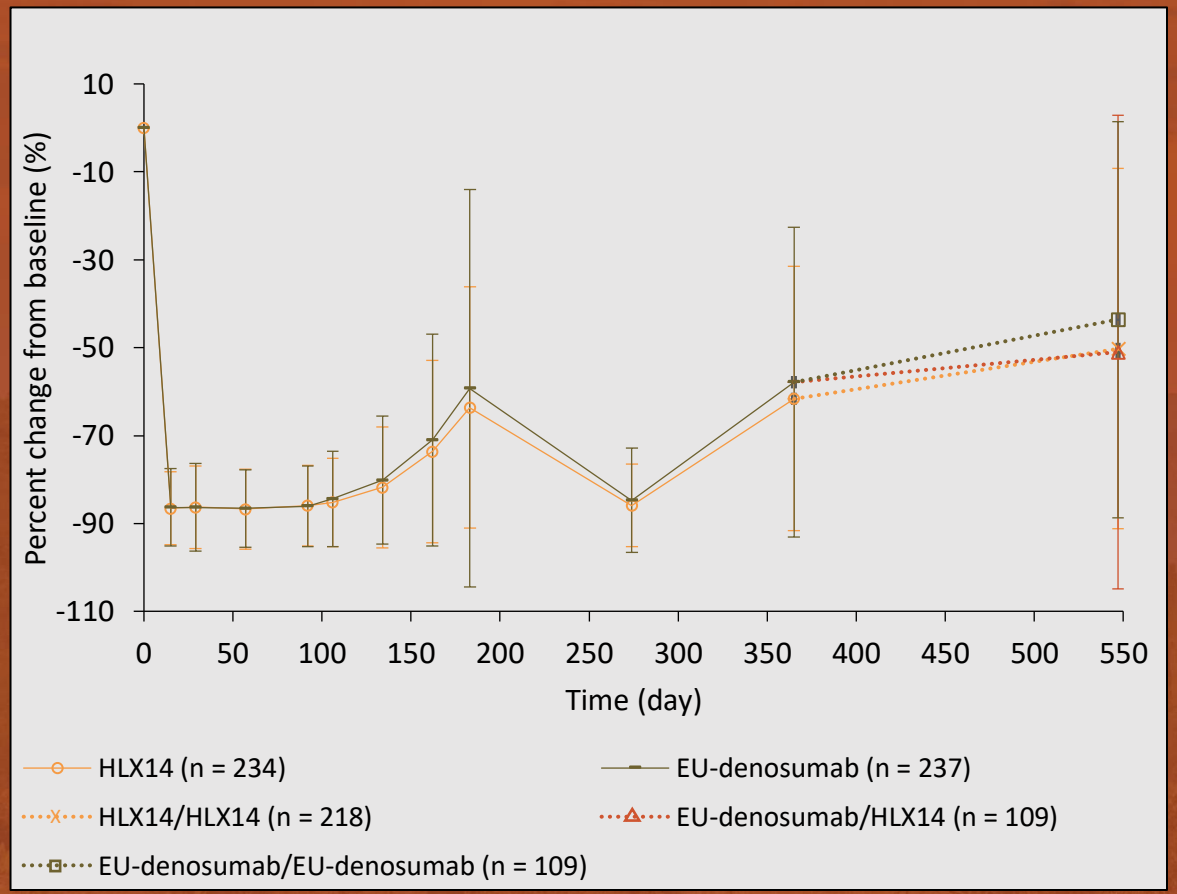
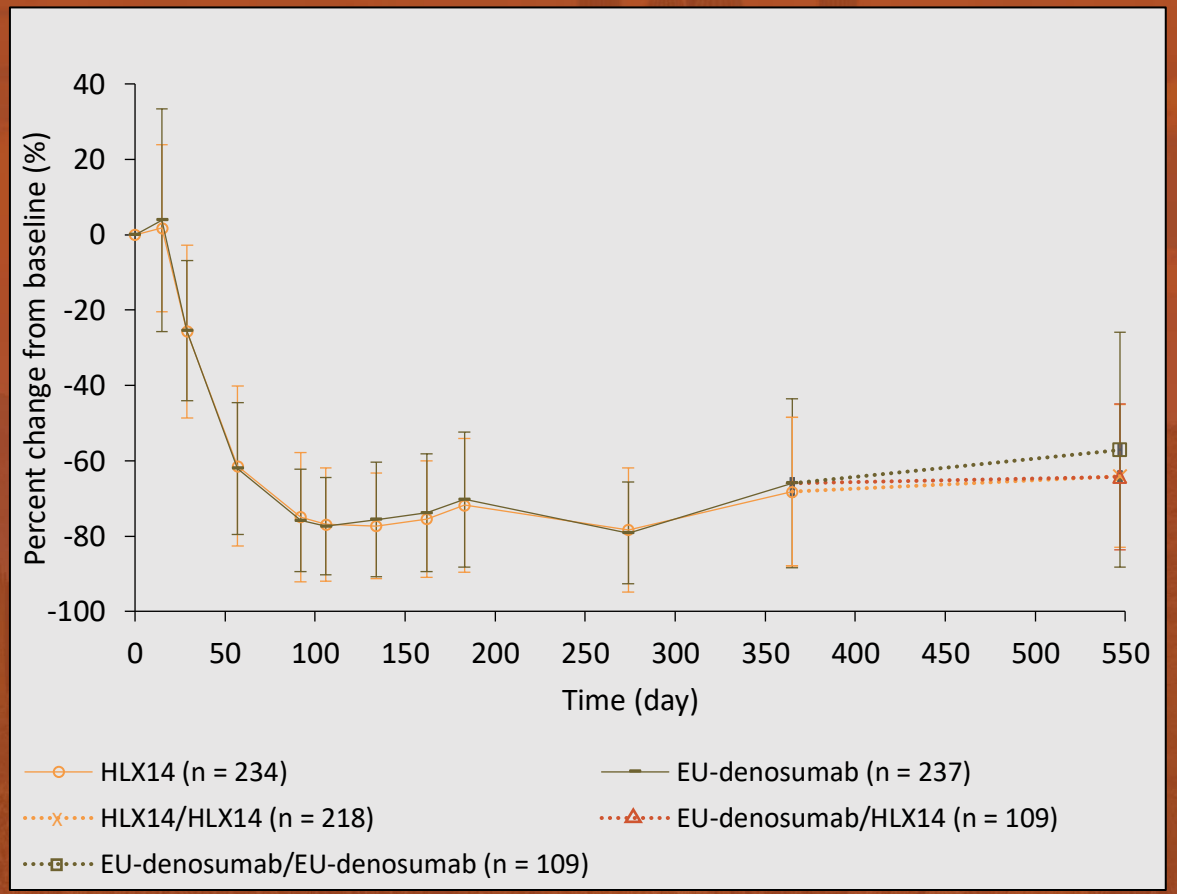
Mean (±SD) for % change from baseline to Week 78 in s-CTX concentration



Mean (±SD) for % change from baseline to Week 78 in s-P1NP concentration



s-CTX, serum type I collagen C-telopeptide; s-P1NP, serum procollagen type 1 N telopeptide.

Safety and Tolerability

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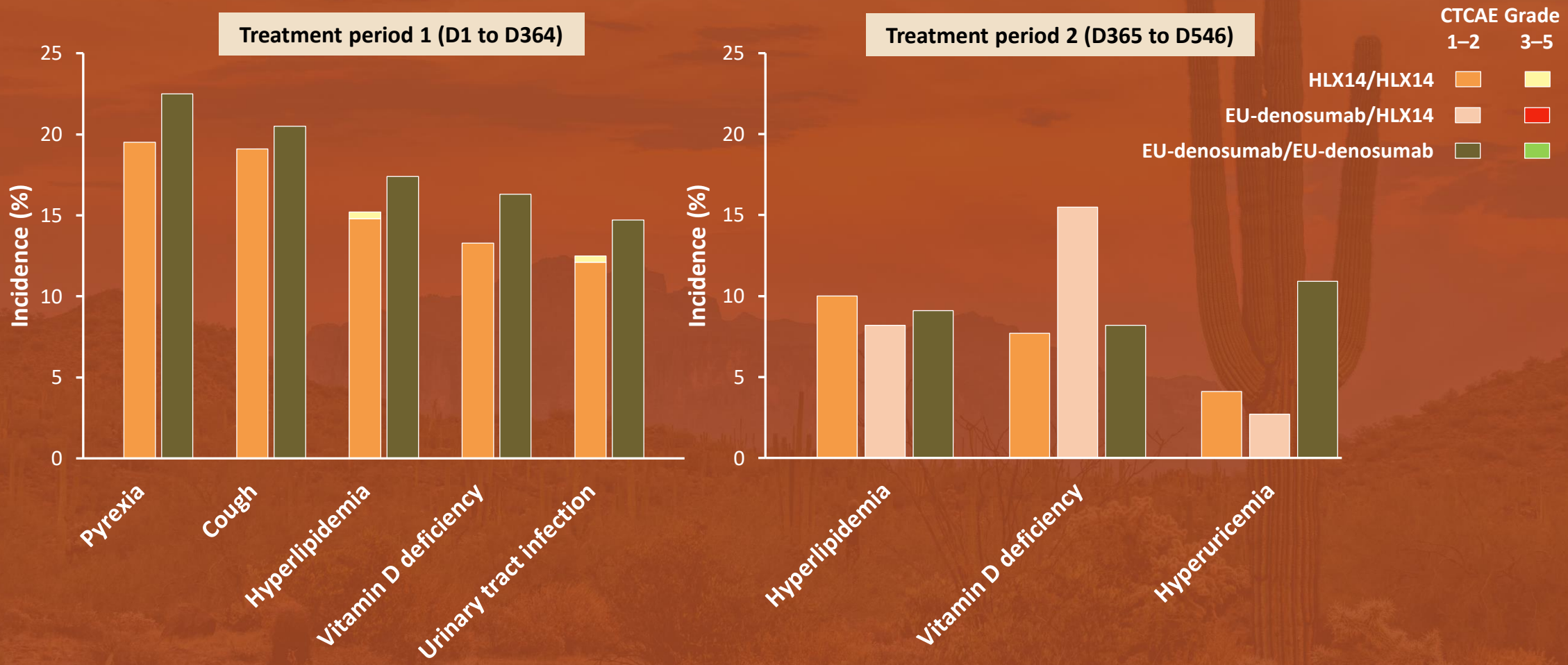
Event, n (%)	Treatment period 1 (D1 to D364)		Treatment period 2 (D365 to D546)		
	HLX14 (N = 256)	EU-denosumab (N = 258)	HLX14/HLX14 (N = 220)	EU-denosumab/ HLX14 (N = 110)	EU-denosumab/ EU-denosumab (N = 110)
Any TEAEs	222 (86.7)	230 (89.1)	153 (69.5)	84 (76.4)	79 (71.8)
Grade 1	103 (40.2)	102 (39.5)	108 (49.1)	64 (58.2)	57 (51.8)
Grade 2	94 (36.7)	109 (42.2)	39 (17.7)	19 (17.3)	16 (14.5)
Grade ≥3	25 (9.8)	19 (7.4)	6 (2.7)	1 (0.9)	6 (5.5)
Serious TEAEs	23 (9.0)	16 (6.2)	6 (2.7)	1 (0.9)	6 (5.5)
Any TEAEs leading to death	0	0	0	0	0
Any TEAEs leading to Tx discontinuation	0	3 (1.2)	0	0	0
Any TRAEs	69 (27.0)	82 (31.8)	25 (11.4)	14 (12.7)	15 (13.6)
Related to HLX14/EU-denosumab	54 (21.1)	65 (25.2)	17 (7.7)	12 (10.9)	8 (7.3)
Grade ≥ 3 TRAEs	3 (1.2)	1 (0.4)	0	0	0
Related to HLX14/EU-denosumab	2 (0.8)	0	0	0	0
Serious TRAEs	3 (1.2)	1 (0.4)	0	0	0
Related to HLX14/EU-denosumab	2 (0.8)	0	0	0	0
Any TRAEs leading to death	0	0	0	0	0
Any TRAEs leading to Tx discontinuation	0	1 (0.4)	0	0	0
Related to HLX14/EU-denosumab	0	1 (0.4)	0	0	0

TEAEs, treatment-emergent adverse events; TRAEs, treatment-related adverse events; Tx, treatment.

Safety and Tolerability

Incidence of TEAEs by PT occurring in ≥10% subjects in the two treatment periods[a]



[a]In any group in either treatment period 1 or treatment period 2.
CTCAE, Common Terminology Criteria for Adverse Events; D, day; PT, preferred terms; TEAEs, treatment-emergent adverse events.

Conclusions

HLX14 demonstrated **efficacy and PD equivalence to EU-denosumab** in postmenopausal women at high fracture risk:

- Comparable improvement of primary efficacy endpoint of LS-BMD, as well as TH-BMD and FN-BMD
- Comparable reduction in incidence of new fractures
- Similar reduction in primary PD endpoint of s-CTX level, as well as s-P1NP level

HLX14 showed **comparable safety profile** with that of EU-denosumab

Equivalence in efficacy, PD, PK, safety, and immunogenicity was observed between HLX14 and reference denosumab, suggesting HLX14 as a proposed biosimilar to denosumab.

FN-BMD, femoral neck bone mineral density; LS-BMD, lumbar spine bone mineral density; LSM, least square mean; PD, pharmacodynamic; s-CTX, serum type I collagen C-telopeptide; SE, standard error; s-P1NP, serum procollagen type 1 N telopeptide; TH-BMD, total hip bone mineral density.

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Thank You
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