ORIGINAL RESEARCH ARTICLE

Efficacy and Safety of Denosumab Biosimilar QL1206 Versus Denosumab in Patients with Bone Metastases from Solid Tumors: A Randomized Phase III Trial

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Abstract

Background Denosumab has been approved for the treatment of bone metastases from solid tumors. QL1206 is the first denosumab biosimilar and needs to be compared with denosumab in a phase III trial.

Objective This phase III trial aims to compare the efficacy, safety, and pharmacokinetics between QL1206 and denosumab in patients with bone metastases from solid tumors.

Methods This randomized, double-blind, phase III trial was conducted in 51 centers in China. Patients aged 18–80 years, with solid tumors and bone metastases, and an Eastern Cooperative Oncology Group performance status of 0–2 were eligible. This study was divided into a 13-week double-blind period, a 40-week open-label period, and a 20-week safety follow-up period. In the double-blind period, patients were randomly assigned (1:1) to receive three doses of QL1206 or denosumab (120 mg subcutaneously every 4 weeks, each). Randomization was stratified by tumor types, previous skeletal-related events, and current systemic anti-tumor therapy. In the open-label period, up to ten doses of QL1206 could be given in both groups. The primary endpoint was percentage change in urinary N-telopeptide/creatinine ratio (uNTX/uCr) from baseline to Week 13. Equivalence margins were $\pm$ 0.135. Secondary endpoints included percentage change in uNTX/uCr at Week 25 and 53, percentage change in serum bone-specific alkaline phosphatase at Week 13, 25, and 53, and time to on-study skeletal-related events. The safety profile was evaluated based on adverse events and immunogenicity.

Results From September 2019 to January 2021, in the full analysis set, 717 patients were randomly assigned to receive QL1206 ($n = 357$) or denosumab ($n = 360$). Median percentage changes in uNTX/uCr at Week 13 in two groups were -75.2% and -75.8%, respectively. Least-squares mean difference in the natural log-transformed ratio of uNTX/uCr at Week 13 to baseline between the two groups was 0.012 (90% confidence interval -0.078 to 0.103), within the equivalence margins. There were no differences in the secondary endpoints between the two groups (all $p > 0.05$). Adverse events, immunogenicity, and pharmacokinetics were similar in the two groups.

Conclusions Denosumab biosimilar QL1206 had promising efficacy, tolerable safety, and pharmacokinetics equivalent to denosumab and could benefit patients with bone metastases from solid tumors.

Clinical Trial Registration ClinicalTrials.gov Identifier: NCT04550949, retrospectively registered on 16 September, 2020

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Key Points

The objective of this phase III trial is to compare the efficacy, safety, and pharmacokinetics between QL1206, the first denosumab biosimilar, and denosumab in patients with bone metastases from solid tumors.

QL1206 was confirmed equivalent to denosumab in efficacy, with similar safety and pharmacokinetic profiles. Switching from denosumab to QL1206 is feasible. QL1206 is an option for patients with bone metastases from solid tumors.

1 Introduction

Bone is a common site for tumor metastasis. Patients with bone metastases have signs of bone destructions and alterations of bone turnover markers (e.g., urinary N-telopeptide/creatinine ratio [uNTX/uCr] and serum bone-specific alkaline phosphatase [s-BALP]). Affected patients can also present with skeletal-related events (SREs) [1, 2]. Skeletal-related events may lead to bone pain and mobility impairment, which result in a decline in quality of life [3].

Denosumab (Xgeva®; Amgen Inc., Thousand Oaks, CA, USA) is an anti-receptor activator of the nuclear factor kappa-B ligand monoclonal antibody [4]. Studies showed denosumab is an effective and safe treatment for preventing SREs and improving quality of life in patients with bone metastatic solid tumors or multiple myeloma [5–10]. Denosumab has been approved for the prevention and treatment of bone metastases from solid tumors by the US Food and Drug Administration and European Medicines Agency [11, 12]. N-telopeptide is a bone turnover marker indicating bone resorption [13]. A research study has shown that the uNTX/uCr level is higher in patients with bone metastatic prostate cancer or lung cancer than that in patients without bone metastases [14]. The change in uNTX/uCr after treatment is associated with SREs, disease progression, and death in patients with bone metastases receiving denosumab [15–17]. These findings suggest that uNTX/uCr is an appropriate surrogate endpoint for SREs.

QL1206 (Qilu Pharmaceutical Co., Ltd., Jinan, China) is the first biosimilar of denosumab, and has the same chemical structure as denosumab. A preliminary phase I trial involving healthy participants has demonstrated the bioequivalence between QL1206 and denosumab [18]. Here, we reported the results of a phase III trial comparing the efficacy, safety profile, and pharmacokinetics (PK) between QL1206 and denosumab in patients with bone metastases from solid tumors.

2 Patients and Methods

2.1 Study Design and Participants

This was a multicenter, randomized, double-blind, phase III trial conducted in 51 centers in China. Patients aged 18–80 years; with histologically or cytologically confirmed solid tumors and bone metastases within 3 months; Eastern Cooperative Oncology Group performance status of 0–2; life expectancy ≥ 3 months; and adequate organ function were eligible. Exclusion criteria included previous treatment with denosumab or bisphosphonates; previous or ongoing osteomyelitis or osteonecrosis of the jaw, active dental or jaw bone disease requiring oral surgery, an unhealed wound after a dental operation or oral surgery, or a planned invasive dental operation, radiotherapy, or surgery to bones.

The study protocol was approved by the ethics committee in each center and registered at ClinicalTrials.gov (identifier NCT04550949). All patients provided written informed consent before participation.

2.2 Study Procedure

The baseline characteristics of patients including age, sex, ethnicity, height, weight, Eastern Cooperative Oncology Group performance status, tumor characteristics, and previous SREs were recorded. The treatment period was divided into a 13-week double-blind period and a 40-week open-label period. The safety follow-up period was 20 weeks. A random allocation sequence was generated by a statistician using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). The patients were randomly assigned 1:1 into the QL1206 or denosumab group, stratified based on tumor types (breast cancer, lung cancer, or the others), previous SREs, and current systemic anti-tumor therapy (yes or no) by investigators using an Interactive Web Response System. In the double-blind period, the patients received three doses of QL1206 or denosumab [120 mg subcutaneously every 4 weeks (Q4W)]. Investigators other than the nurses who administer the study drugs were blinded to allocation. The data of the primary endpoint was obtained at the end of the double-blind period. In the open-label period, to evaluate the long-term efficacy and safety of QL1206 and the feasibility of switching from denosumab to QL1206, up to 10 further doses of QL1206 (120 mg subcutaneously Q4W) can be given at the discretion of investigators in both groups. The patients also received daily supplementation of calcium (≥ 500 mg) and vitamin D (≥ 400 U) throughout the treatment period. All cancer-specific therapies were allowed, except for bisphosphonates or unapproved investigational treatments.

The uNTX and s-BALP levels were measured in the central laboratory (Guangzhou Kingmed Diagnostics Group

Co., Ltd., Guangzhou, China) at baseline, at Week 2, 5, 13, 25, 37, and 53, and at study treatment discontinuation, using an enzyme-linked immunosorbent assay [19] and the Access Ostase assay (Beckman Coulter Inc., Brea, CA, USA) [20], respectively. SREs, which were defined as pathologic fractures, spinal cord compression, or requirements for radiation or surgery of bones, were assessed throughout the treatment period.

Adverse events (AEs) were evaluated from study treatment initiation to the end of the safety follow-up period according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Immunogenicity was evaluated through measuring the serum anti-drug antibody (ADA) levels in the central laboratory (Shanghai Xihua Scientific Co., Ltd., Shanghai, China) at Week 5, 13, 25, and 53, and at study treatment discontinuation, using a semi-quantitative electrochemiluminescent assay. Those with positive ADA results received further tests for the neutralizing antibody (Nab) by a semi-quantitative electrochemiluminescent Nab assay.

For the population PK (popPK) analysis, the data from the phase I trial of QL1206 in healthy subjects (80 for QL1206 and 76 for denosumab) [18] and the present trial were used. In the present study, the serum samples were collected at Week 1, 5, 9, 10, 11, 12, 13, 25, and 53. Drug concentrations were tested in the same laboratory as ADA detection using an enzyme-linked immunosorbent assay.

2.3 Outcomes

The primary endpoint was the percentage change in uNTX/uCr from baseline to Week 13. The secondary endpoints included percentage change in uNTX/uCr from baseline to Week 25 and 53, the percentage change in s-BALP from baseline to Week 13, 25, and 53, and the time to first on-study SRE. The safety endpoints were AEs and immunogenicity. The exploratory endpoint was popPK.

2.4 Statistical Analysis

It is assumed that the natural log-transformed uNTX/uCr ratio of Week 13 to baseline [=$\ln(\text{uNTX/uCr}_{Week13} \div \text{uNTX/uCr}_{baseline})$] was equal between the two groups. In total, 598 patients (299 each group) were required for 80% power with a pooled standard deviation of 0.56 and equivalence margins of $\pm$ 0.135 based on a 90% two-sided confidence interval (CI). Considering a possible 15% dropout rate, a sample size of 700 patients (350 each group) was needed.

All statistical analyses were performed using SAS version 9.4. For the primary endpoint, according to the Statistical Guideline of Bioequivalence Study of National Medical Products Administration of China [21], a p-value of < 0.05 for two one-sided tests was considered statistically

significant. For the secondary endpoints, a two-sided p-value of < 0.05 was considered statistically significant. The analysis set should be as close as possible to the intention-to-treat ideal [22]. Thus, the primary and secondary endpoints were evaluated in the full analysis set (FAS), including all randomized patients receiving at least one dose of the study drug and one efficacy evaluation. The per-protocol set (PPS) was used for the sensitivity analyses, and included patients in the FAS without a major protocol violation. The safety endpoints were summarized by treatment group in the safety set, which included patients receiving at least one dose of the study drug and one post-baseline safety evaluation.

Comparison of the primary endpoint between the two groups was performed using an analysis of covariance on the natural log-transformed uNTX/uCr ratio of Week 13 to baseline. The treatment group and randomization strata were independent variables and the baseline uNTX/uCr was a covariate, with equivalence margins of $\pm$ 0.135. Missing data were imputed using the last observation carried forward method for subjects with a post-baseline assessment. Predefined subgroup analyses of the primary endpoint were based on age, sex, and randomization strata. Further, to minimize the center effect, a serial number of centers was included as an additional independent variable in the analysis of covariance model for a post-hoc sensitivity analysis.

Changes in uNTX/uCr at the other timepoints were analyzed using the same methods as the primary endpoint, except missing data were not imputed. The percentage changes in s-BLAP were compared using a van Elteren test adjusted by randomization strata. The median time to the first on-study SRE was estimated by the Kaplan–Meier method and Greenwoods' formula. Hazard ratios were calculated using a Cox proportional hazards model adjusted by randomization strata.

PopPK was analyzed in the patients receiving at least one dose of the study drug and one drug concentration evaluation in the present study (i.e., popPK analysis set). The PK model was established based on the healthy subjects in the phase I study [18]. PopPK modeling was conducted through NONMEM version 7.4 (Icon Development Solutions, LLC, Ellicott City, MD, USA) using standard model building and evaluation approaches. Covariates, including disease state (healthy subject or patient), treatment group, age, sex, baseline body weight, baseline estimated glomerular filtration rate, baseline aspartate aminotransferase, baseline alanine aminotransferase, baseline alkaline phosphatase, baseline albumin, and ADA were evaluated to determine the association with PK. Nonlinear mixed-effects modeling was used to estimate the PK parameters. The final model was evaluated using visual predictive checks. Based on the established popPK model, the maximum a posteriori Bayesian method was used to estimate the individual PK parameters of patients. PK

bioequivalence was also judged using the 90% CI of the ratio of a log-transformed exposure measure (the area under the serum drug concentration-time curve [AUC] from $t = 0$ to Week 4 after a single dose [$AUC_{0-4 \, week,1}$], maximum serum drug concentration after a single dose [$C_{max,1}$], AUC from $t = 0$ to Week 4 at steady-state [$AUC_{0-4 \, week,ss}$], and maximum serum drug concentration at steady-state [$C_{max,ss}$]; equivalence margins: 80–125%).

3 Results

3.1 Patient Enrollment and Baseline Characteristics

From September 2019 to January 2021, 853 patients were screened and 728 were randomized to the two groups (364 patients in each group). The FAS included 717 patients (357 and 360 patients in the QL1206 and denosumab groups, respectively). The PPS included 646 patients (321 and 325 patients in the QL1206 and denosumab groups, respectively; Fig. 1). The baseline characteristics were not statistically significant different between the two groups (Table 1).

3.2 Efficacy Analyses

In the FAS, the median percentage changes in uNTX/uCr at Week 13 were − 75.2% (− 86.8%, − 53.5%) for QL1206 and − 75.8% (− 87.3%, − 48.7%) for denosumab (Fig. 2A). The analysis of covariance showed the least-squares means (LSMs) of natural log-transformed uNTX/uCr ratio of Week 13 to baseline were − 1.429 (standard error 0.130) and − 1.441 (0.130) in the QL1206 group and denosumab group, respectively. The LSM difference between the two groups was 0.012 (0.055; 90% CI − 0.078 to 0.103; $p = 0.8208$; Fig. 2B) within the equivalence margins of ±0.135. The results at Week 25 and 53 also showed a similarity between the two groups (Fig. 2A, B). There were parallel trends of the decline in s-BALP in the two groups (Fig. 2C). No significant difference in the percentage change at each timepoint was observed between the two groups (all $p > 0.05$). At Week 53, the SRE rates were low and numerically similar between the two groups (34 [9.5%] and 30 [8.3%] events in the QL1206 and denosumab groups, respectively). In both the groups, the most common SRE was pathological fracture (22 [6.2%] and 14 [3.9%] events). The time to the first on-study SRE was immature (Table S1 of the Electronic Supplementary Material [ESM]). The QL1206 group had a hazard ratio of 1.163 (95% CI 0.711–1.900; $p = 0.5478$; Fig. 3) compared with the denosumab group. The PPS showed consistent results of all efficacy endpoints (uNTX/uCr, s-BALP, and SRE) between the QL1206 and denosumab groups (Table S2 of the ESM).

The results of the predefined subgroup analyses for comparison of the primary endpoint are shown in Fig. S1 of the ESM. No significant difference between the two groups was observed, except in the subgroup of patients without

Fig. 1 Trial flowchart
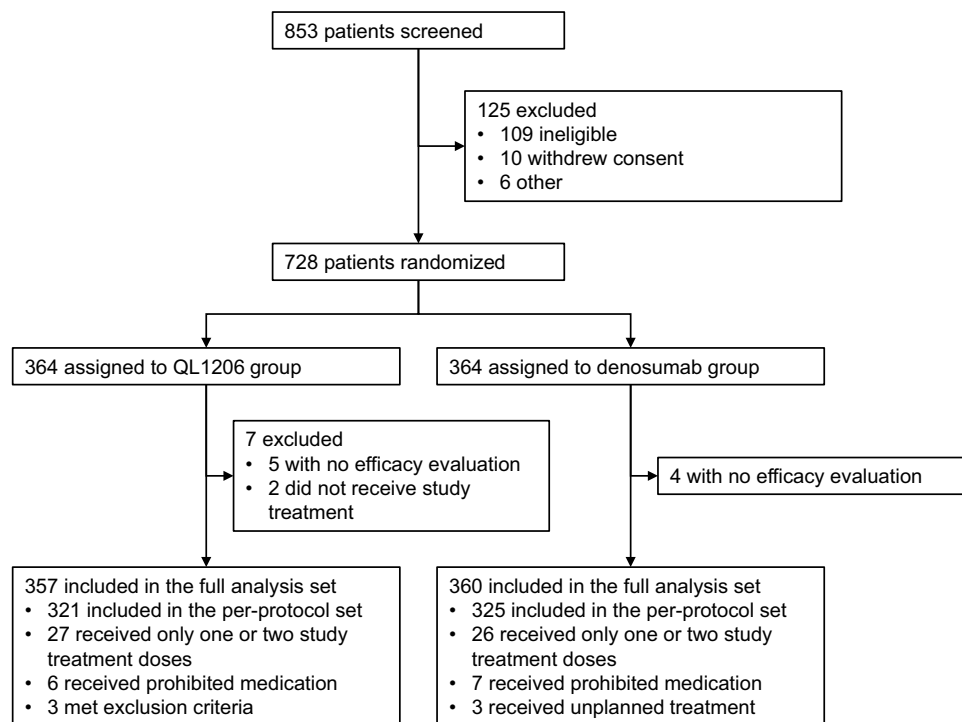
Table 1 Baseline demographics and tumor characteristics (full analysis set)

	QL1206 group (n = 357)	Denosumab group (n = 360)
Age, years	56.4 ± 9.9	56.8 ± 10.8
≤ 60	231 (64.7%)	211 (58.6%)
> 60	126 (35.3%)	149 (41.4%)
Sex		
Male	129 (36.1%)	109 (30.3%)
Female	228 (63.9%)	251 (69.7%)
Ethnicity		
Han	337 (94.4%)	335 (93.1%)
Others	20 (5.6%)	25 (6.9%)
BMI, kg/m^2	23.4 ± 3.5	23.5 ± 3.4
ECOG performance status		
0	69 (19.3%)	91 (25.3%)
1	271 (75.9%)	254 (70.6%)
2	17 (4.8%)	15 (4.2%)
uNTX/uCr, nmoL/mmoL	78.2 ± 95.8	78.6 ± 87.6
s-BALP, U/L	28.4 ± 45.3	27.0 ± 37.3
Tumor types		
Lung cancer	200 (56.0%)	198 (55.0%)
Breast cancer	151 (42.3%)	156 (43.3%)
Others	6 (1.7%)	6 (1.7%)
Site of metastases[a]		
Bone	357 (100%)	360 (100%)
Lymph node	212 (59.4%)	216 (60.0%)
Lung	113 (31.7%)	110 (30.6%)
Liver	72 (20.2%)	53 (14.7%)
Pleura	53 (14.8%)	64 (17.8%)
Brain	28 (7.8%)	25 (6.9%)
Kidney	8 (2.2%)	3 (0.8%)
Meninges	3 (0.8%)	1 (0.3%)
Others	60 (16.8%)	62 (17.2%)
Number of metastases		
1	77 (21.6%)	75 (20.8%)
2	120 (33.6%)	130 (36.1%)
≥ 3	160 (44.8%)	155 (43.1%)
Previous SREs	56 (15.7%)	55 (15.3%)
Current systemic anti-tumor therapy	354 (99.2%)	355 (98.6%)

Data are presented as mean ± standard deviation or number (%)

BMI body mass index (calculated as weight in kg divided by height in m^2), *ECOG* Eastern Cooperative Oncology Group, *uNTX/uCr* urinary N-telopeptide/creatinine ratio, *s-BALP* serum bone-specific alkaline phosphatase, *SREs* skeletal-related events

[a]Multiple sites of metastases per patient are possible

current systemic anti-tumor therapy. However, this subgroup comprised only 13 patients (six for QL1206 and seven for denosumab). The post-hoc sensitivity analysis for the center effect showed the LSM difference of 0.008 (0.055; 90% CI − 0.082 to 0.098; *p* = 0.8860) between the two groups, consistent with the primary analysis.

3.3 Safety Analysis

Among the 717 patients included in the SS, 707 (98.6%) patients had a treatment-emergent AE (TEAE), with 351/356 (98.6%) and 356/361 (98.6%) patients having a TEAE in the QL1206 and denosumab groups, respectively. The most common TEAEs were anemia (37.6% and 36.3%), white blood cell count decreased (34.0% and 36.6%), neutrophil count decreased (33.7% and 36.6%), aspartate aminotransferase increased (31.2% and 33.5%), and alanine aminotransferase increased (30.9% and 32.1%). TEAEs ≥ grade 3 (48.9% and 51.0%) and treatment-emergent serious AEs (19.7% and 20.5%) were similar between the groups. Neutrophil count decreased (15.4% and 15.0%), disease progression (8.4% and 8.3%), and white blood cell count decreased (7.6% and 9.1%) were the most common TEAEs ≥ grade 3. Study treatment discontinuation because of a TEAE was reported in eight (2.2%) patients for QL1206 and 11 (3.0%) for denosumab. There were 18 (5.1%) and 22 (6.1%) patients who experienced a TEAE leading to death in the QL1206 and denosumab groups, respectively. No death was considered treatment related (Table 2).

In total, 697 patients were included in the immunogenicity analysis (345 in the QL1206 group and 352 in the denosumab group). At Week 53, 15 (4.3%) patients in the QL1206 group and 18 (5.1%) patients in the denosumab group had positive ADA results. Six patients (3 [0.9%], each) had positive Nabs.

3.4 PopPK Analysis

The PK of QL1206 and denosumab in healthy subjects and patients with bone metastases from solid tumors were best described by a one-compartment model with Michaelis-Menten kinetics. The final model parameters were estimated with acceptable precision (Table S3 of the ESM). The results of visual predictive checks indicated that the model had excellent predictive ability to describe the QL1206 and denosumab concentrations. Overall, the model appeared to adequately characterize the PK of QL1206 and denosumab

Fig. 2 Urinary N-telopeptide/creatinine ratio (uNTX/uCr) and serum bone-specific alkaline phosphatase (s-BALP) data in the full analysis set. **A** Median percentage changes from baseline (BL) in uNTX/uCr; **B** Least-squares means (LSM) of natural log-transformed ratio of uNTX/uCr at each timepoint to BL analyzed using one-sided analysis of covariance. Treatment group and the randomization strata were independent variables and BL uNTX/uCr was a covariate. Missing data at Week 13 were imputed using the last observation carried forward method for subjects with a post-BL assessment. The difference at Week 13 was within the equivalence margins ($p = 0.8208$). No significant difference between the two groups was observed at Week 25 and 53 ($p = 0.5905$ and 0.1640); **C** Median percentage changes from BL in s-BALP. A van Elteren test adjusted by the randomization strata was used for comparison between the two groups. No significant difference between the two groups was observed at Week 13, 25, and 53 ($p = 0.9585$, 0.6681, and 0.4872). Urine and blood samples were tested for uNTX/uCr and s-BALP, respectively. Numbers of patients with available uNTX/uCr and s-BALP data differed because of the different numbers of patients with missed sampling or a missed time window. *W* Week, *SE* standard error
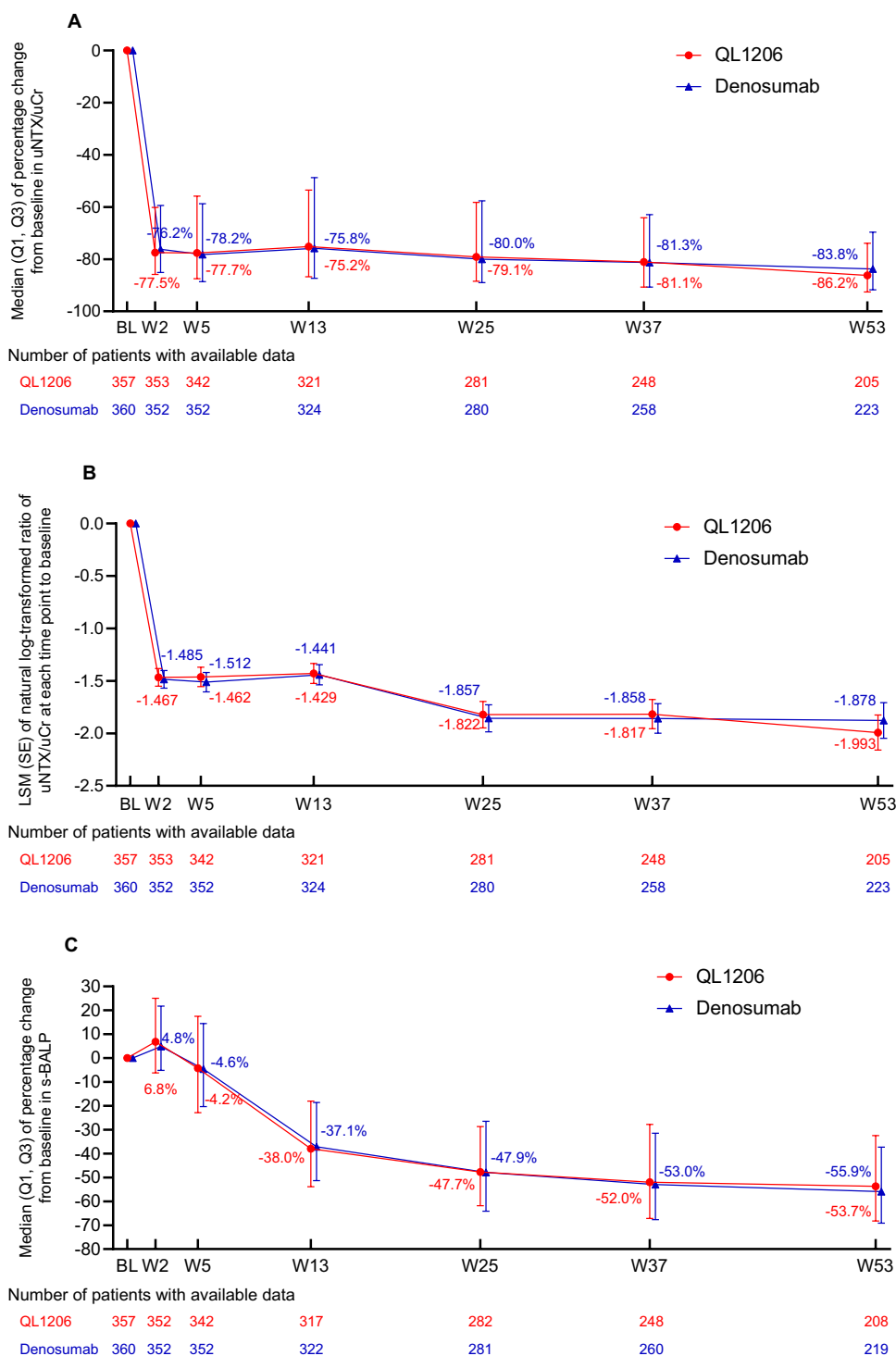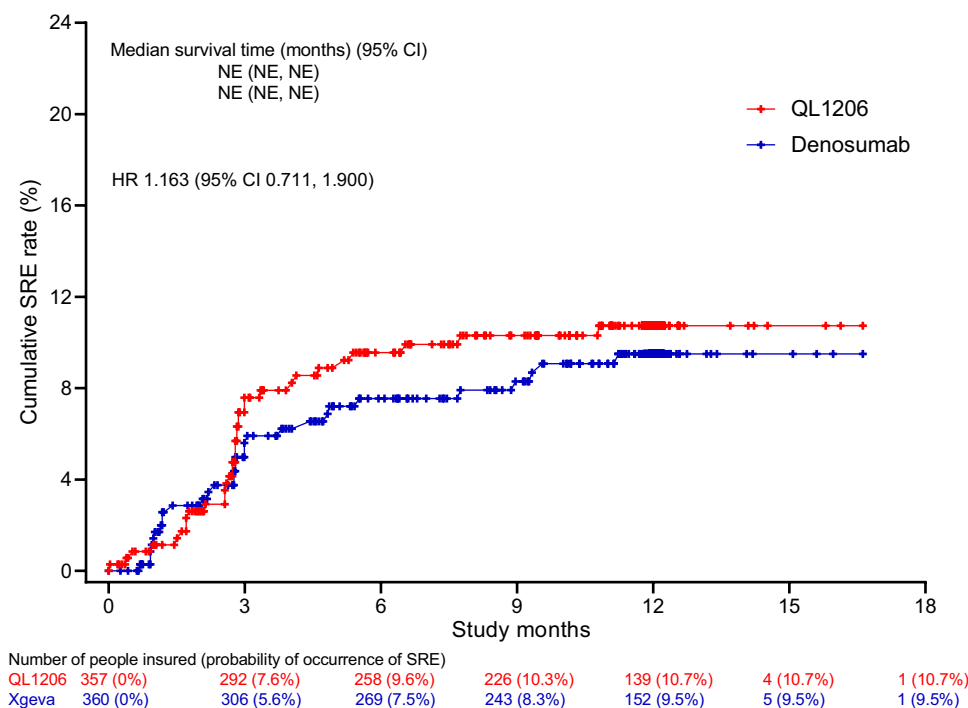

and was suitable to explore any covariate effects on the PK of QL1206 and denosumab (Figure S2 of the ESM).

The maximum a posteriori Bayesian method was used to estimate the exposure parameters of patients with bone metastasis. For QL1206, the geomean of $AUC_{0-4 \text{ week},1}$ and $C_{max,1}$ after a single dose were 230 mg·day/L and 9.92

mg/mL, respectively. For the steady-state exposure, the geomean of $AUC_{0-4 \text{ week},ss}$ and $C_{max,ss}$ were 655 mg·day/L and 27.0 mg/mL, respectively. For denosumab, the geomean of $AUC_{0-4 \text{ week},1}$ and $C_{max,1}$ after a single dose were 217 mg·day/L and 9.42 mg/mL, while for the steady-state exposure, the geomean of $AUC_{0-4 \text{ week},ss}$ and $C_{max,ss}$

Fig. 3 Cumulative skeletal-related event (SRE) rates in the two groups. Median survival time was not estimable (NE). A Cox proportional hazards model adjusted by the randomization strata was used for comparison between the two groups. No significant difference between the groups was observed ($p = 0.5478$). *HR* hazard ratio, *CI* confidence interval

Median survival time (months) (95% CI)
NE (NE, NE)
NE (NE, NE)

HR 1.163 (95% CI 0.711, 1.900)

Number of people insured (probability of occurrence of SRE)
QL1206 357 (0%) 292 (7.6%) 258 (9.6%) 226 (10.3%) 139 (10.7%) 4 (10.7%) 1 (10.7%)
Xgeva   360 (0%) 306 (5.6%) 269 (7.5%) 243 (8.3%)   152 (9.5%)   5 (9.5%)   1 (9.5%)

were 564 mg·day/L and 23.5mg/mL, respectively. The 90% CI of the geometric mean ratios of above exposure ($AUC_{0–4\ week,1}$, $C_{max,1}$, $AUC_{0–4\ week,ss}$, and $C_{max,ss}$) between the QL1206 group and denosumab group were within the equivalence margins of 80–125%.

4 Discussion

The present double-blind phase III trial showed that QL1206, the first denosumab biosimilar, had a clinical efficacy and safety profile comparable to denosumab. This was also the first study using the surrogate endpoint uNTX/uCr as the primary endpoint to evaluate the efficacy of a denosumab biosimilar. We further studied the immunogenicity and PK of QL1206 and proved its similarity to denosumab.

The key strength of the present study is that the surrogate endpoint uNTX/uCr was chosen as the primary endpoint. N-telopeptide is a proteolytic product of type I collagen (a major component of bone matrix) and indicates bone resorption [13]. The uNTX/uCr is a commonly used biomarker in patients with bone metastatic diseases. In bone metastatic prostate cancer or lung cancer, uNTX/uCr was higher than that in patients without bone metastases [14]. Higher NTX at baseline suggests a higher risk of a negative outcome in patients who do not receive bone antiresorptive agents [14]. Previous studies reported that uNTX/uCr reduction after treatment was also associated with a lower

risk of SRE, disease progression, and death in patients with bone metastases receiving denosumab or bisphosphonates [15, 16]. A meta-regression analysis produced similar conclusions [17]. These results indicated that uNTX/uCr can be used as a surrogate endpoint for SRE in patients with bone metastases from solid tumors. Regulatory guidelines of the National Medical Products Administration of China, US Food and Drug Administration, and European Medicines Agency also supported a biomarker as the primary endpoint in a trial of a biosimilar versus the reference. [23–25] Additionally, in a previous phase III study of denosumab versus zoledronic acid [26] and two ongoing phase III studies of denosumab biosimilars versus the reference in patients with bone metastases (NCT04812509 and NCT04859569), the percentage change in uNTX/uCr from baseline to Week 13 was also used as the primary endpoint. Thus, uNTX/uCr was chosen as the primary endpoint of the present study. We found a 75.8% decrease in uNTX/uCr after denosumab treatment at Week 13, consistent with the results of previous studies (81.9% decrease) [26]. QL1206 also had uNTX/uCr changes parallel to that produced by denosumab. Subgroup analyses of the change in uNTX/uCr at Week 13 showed that, except for the subgroup without current systemic anti-cancer therapy, all the other subgroups of age, sex, tumor type, previous SRE, and current systemic anti-tumor therapy had similar changes in uNTX/uCr between the two groups. The subgroup without current systemic anti-tumor therapy comprised only 13 patients, which might have produced bias

Table 2 Adverse events (safety set)

	QL1206 group (n = 356)	Denosumab group (n = 361)
All TEAEs	351 (98.6%)	356 (98.6%)
Treatment related	254 (71.3%)	270 (74.8%)
TEAE ≥ grade 3	174 (48.9%)	184 (51.0%)
Treatment related	33 (9.3%)	41 (11.4%)
TEAE leading to study drug suspension	16 (4.5%)	23 (6.4%)
Treatment related	8 (2.2%)	7 (1.9%)
TEAE leading to study drug discontinuation	8 (2.2%)	11 (3.0%)
Treatment related	4 (1.1%)	3 (0.8%)
TESAE	70 (19.7%)	74 (20.5%)
Treatment related	1 (0.3%)	3 (0.8%)
TEAE leading to death	18 (5.1%)	22 (6.1%)
Treatment related	0	0
TEAE in > 20% patients in either treatment group		
Anemia	134 (37.6%)	131 (36.3%)
White blood cell count decreased	121 (34.0%)	132 (36.6%)
Neutrophil count decreased	120 (33.7%)	132 (36.6%)
Aspartate aminotransferase increased	111 (31.2%)	121 (33.5%)
Alanine aminotransferase increased	110 (30.9%)	116 (32.1%)
Hypocalcemia	99 (27.8%)	116 (32.1%)
Hypophosphatemia	82 (23.0%)	95 (26.3%)
Platelet count decreased	82 (23.0%)	91 (25.2%)
Blood parathyroid hormone increased	78 (21.9%)	89 (24.7%)
Hypoproteinemia	74 (20.8%)	74 (20.5%)
Hypertriglyceridemia	74 (20.8%)	74 (20.5%)
TEAE ≥ grade 3 in > 5% patients in either treatment group		
Neutrophil count decreased	55 (15.4%)	54 (15.0%)
Disease progression	30 (8.4%)	30 (8.3%)
White blood cell count decreased	27 (7.6%)	33 (9.1%)
Anemia	24 (6.7%)	25 (6.9%)
Hypophosphatemia	20 (5.6%)	26 (7.2%)
Platelet count decreased	16 (4.5%)	20 (5.5%)

Data are presented as n (%)

TEAE treatment-emergent adverse event, *TESAE* treatment-emergent serious adverse event

in the analysis. Further, the result of the sensitivity analysis for center effect was comparable to the primary analysis, indicating the center effect could be neglected.

Patients with SREs experienced pain and decreased quality of life [3]. Denosumab decreases the incidence of SREs and delays the time to SREs [6–8]. Although the SRE data were immature after the 53-week follow-up period in the present study, the time to the first on-study SRE was similar between the two treatments, indicating that QL1206 and denosumab had equivalent efficacy in both bone turnover markers and SREs. The incidences of SREs were comparable between the QL1206 (9.5%) and denosumab treatments (8.3%), but were slightly higher than previous results of

denosumab (4.9%) [26]. This may be because of an insufficient event number and/or different baseline characteristics in the two trials.

In previous studies, approximately 97% of patients receiving denosumab reported TEAEs [6–8]. Our present study showed similar incidences of TEAEs. Both treatments reported an incidence of 98.6%. Previous studies found denosumab can cause an electrolyte imbalance (e.g., hypocalcemia and hypophosphatemia) [27, 28]. Similar frequencies of hypocalcemia and hypophosphatemia were observed between two groups in the present study. Other categories of AEs (e.g., ≥ grade 3 TEAEs) were also similar between

the two groups. All these results suggested that QL1206 and denosumab have similar safety profiles.

Indeed, when QL1206 is approved, patients will have more choice to receiving either denosumab or QL1206. Previous studies have revealed increased discontinuation rates after switching other references drugs to biosimilars, mainly owing to nocebo effects [29]. After the double-blind period in the present study, all patients received QL1206 to assess the long-term efficacy and safety of QL1206 and the feasibility of switching from denosumab to QL1206. The changes in uNTX/uCr and s-BALP from baseline to Week 25 and 53 as well as the on-study SRE throughout Week 53 were similar between the two groups. Adverse events were tolerable. The incidences of TEAEs leading to treatment discontinuation were low (2.2% and 3.0%). Thus, the nocebo effect was considered not clinically relevant. This evidence strongly suggests that the QL1206 has clinical efficacy and safety equivalent to denosumab, and that switching from denosumab to QL1206 is feasible.

Denosumab is an antibody with the potential to stimulate host immune responses [30]. The preliminary phase I trial showed that 7.4% and 4.0% of healthy participants developed antibodies after QL1206 and denosumab treatment, respectively. [18] No Nab was identified in the healthy participants. In the present study, we found that similar percentages of patients had positive antibodies after QL1206 and denosumab treatment. The levels of antibodies were low, suggesting a low immunogenicity of the two drugs. In addition, similar percentages of patients had Nabs between the two groups. The significance of Nabs in patients with cancer but not in the healthy participants requires further investigation.

Although a popPK analysis of denosumab has been previously reported [31, 32], a popPK model of a denosumab biosimilar based on a comparative clinical study in patients with cancer has not been established. In the present study, the popPK analysis identified treatment, weight, and albumin as significant covariates influencing systemic clearance in the central compartment, and disease state, weight, and albumin as significant covariates influencing volume of distribution in the central compartment. However, the effects of covariates on exposure were not clinically meaningful, leading to a recommendation for no dose adjustments when administering QL1206 or denosumab to patients with bone metastases from solid tumors at the dosage of 120 mg Q4W. Model-based simulations demonstrated QL1206 (120 mg Q4W) is bioequivalent to denosumab.

This study has several limitations. First, this study only enrolled Chinese patients and most patients had lung cancer or breast cancer. Thus, caution must be paid when these results were interpreted for patients with other ethnicities or with bone metastases from other solid tumors. Second, the SRE data were immature because of an insufficient follow-up duration. Nevertheless, according to the protocol, the present study has already ended and the SRE results will not be updated. Third, we can only provide LSMs for uNTX/uCr and a hazard ratio for SRE, but not a risk difference or ratio, according to data type.

5 Conclusions

As the first denosumab biosimilar, QL1206 has promising clinical efficacy in the reduction of uNTX/uCr, s-BALP, and the risk of SREs, and a tolerable safety profile, immunogenicity, and PK similar to denosumab. Switching from denosumab to QL1206 is feasible. QL1206 is an option for patients with bone metastases from solid tumors.

Declarations

Conflicts of Interest/Competing Interests Cuicui Han, Yunjie Li, and Xiaoyan Kang are employees of Qilu Pharmaceutical Co., Ltd. All the other authors have no conflicts of interest that are directly relevant to the content of this article.

Ethics Approval The study protocol was approved by the ethics committee in each center.

Consent to Participate All patients provided written informed consent before participation.

Consent for Publication Not applicable.

Availability of Data and Material The datasets generated during and/or analyzed during the current study are not publicly available because we may further analyze the raw data for other research objectives.

Code Availability Not applicable.

Authors' Contributions HL and LZ had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: HL, YH, CH, XK, LZ. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: HL, YH, LZ. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: YL. Obtained funding: HL, XK, LZ. Administrative, technical, or material support: CH, XK. Supervision: HL, XK, LZ.

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