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Efficacy, Safety, and Population Pharmacokinetics of MW032 Compared With Denosumab for Solid Tumor–Related Bone Metastases

A Randomized, Double-Blind, Phase 3 Equivalence Trial

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IMPORTANCE The bioequivalence of denosumab biosimilar has yet to be studied in a 53-week, multicenter, large-scale, and head-to-head trial. A clinically effective biosimilar may help increase access to denosumab in patients with solid tumor–related bone metastases.

OBJECTIVES To establish the biosimilarity of MW032 to denosumab in patients with solid tumor–related bone metastases based on a large-scale head-to-head study.

DESIGN, SETTING, AND PARTICIPANTS In this 53-week, randomized, double-blind, phase 3 equivalence trial, patients with solid tumors with bone metastasis were recruited from 46 clinical sites in China. Overall, 856 patients were screened and 708 eligible patients were randomly allocated to receive either MW032 or denosumab.

INTERVENTIONS Patients were randomly assigned (1:1) to receive MW032 or reference denosumab subcutaneously every 4 weeks until week 49.

MAIN OUTCOMES AND MEASURES The primary end point was percentage change from baseline to week 13 of natural logarithmic transformed urinary N-telopeptide/creatinine ratio (uNTx/uCr).

RESULTS Among the 701 evaluable patients (350 in the MW032 group and 351 in the denosumab group), the mean (range) age was 56.1 (22.0-86.0) years and 460 patients were women (65.6%). The mean change of uNTx/uCr from baseline to week 13 was −72.0% (95% CI, −73.5% to −70.4%) in the MW032 group and −72.7% (95% CI, −74.2% to −71.2%) in the denosumab group. These percent changes corresponded to mean logarithmic ratios of −1.27 and −1.30, or a difference of 0.02. The 90% CI for the difference (−0.04 to 0.09) was within the equivalence margin (−0.13 to 0.13); the mean changes of uNTx/uCr and bone-specific alkaline phosphatase (s-BALP) at each time point were also similar during 53 weeks. The differences of uNTx/uCr change were 0.015 (95% CI, −0.06 to 0.09), −0.02 (95% CI, −0.09 to 0.06), −0.05 (95% CI, −0.13 to 0.03) and 0.001 (95% CI, −0.10 to 0.10) at weeks 5, 25, 37, and 53, respectively. The differences of s-BALP change were −0.006 (95% CI, 0.06 to 0.05), 0.00 (95% CI, −0.07 to 0.07), −0.085 (95% CI, −0.18 to 0.01), −0.09 (95% CI, −0.20 to 0.02), and −0.13 (95% CI, −0.27 to 0.004) at weeks 5, 13, 25, 37 and 53, respectively. No significant differences were observed in the incidence of skeletal-related events (−1.4%; 95% CI, −5.8% to 3.0%) or time to first on-study skeletal-related events (unadjusted HR, 0.86; $P = .53$; multiplicity adjusted HR, 0.87; $P = .55$) in the 2 groups.

CONCLUSIONS AND RELEVANCE MW032 and denosumab were biosimilar in efficacy, population pharmacokinetics, and safety profile. Availability of denosumab biosimilars may broaden the access to denosumab and reduce the drug burden for patients with advanced tumors.

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Visual Abstract

Supplemental content

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Metastatic bone disease (MBD) is a frequent complication of cancer that affects more than 1.5 million patients worldwide,[1] particularly patients with breast and prostate cancer. Retrospective studies have reported that bone metastases were found in 73% of patients with breast cancer and 68% of patients with prostate cancer. Incidence was also high in thyroid cancer (60%) and lung cancer (30%-40%).[2] Patients frequently experienced osteoclast-mediated bone destruction that resulted in clinically important complications, such as fracture, need for bone radiation or surgery, spinal cord compression, hypercalcemia, or bone pain.[3] These complications, collectively known as skeletal-related events (SREs), are associated with considerable morbidity and poor prognosis in patients with advanced cancer. The 5-year survival rate was 75.8% for patients with breast cancer without bone metastases, whereas it was only 8.3% for patients with bone metastases, and 2.5% for those with both bone metastases and SREs.[4] SREs are also associated with severely impaired quality of life due to increased pain, reduced physical function and loss of autonomy.[5] Thus, preventing SREs has important clinical significance in the treatment of malignant bone metastases.

Denosumab was the first human monoclonal antibody with high affinity and specificity for the soluble and cell membrane-bound forms of human RANKL.[6] After binding to RANKL, it inhibits the maturation, differentiation, and function of osteoclasts, reduces bone absorption and destruction, and increases bone mineral density.[7] Like other monoclonal antibodies, denosumab mainly relies on the endothelial reticulum system for clearance, without going through the kidneys, so it generally does not cause kidney insufficiency.[8] It can be used in patients with severe kidney impairment, such as chronic kidney disease, providing an available approach to other inapplicable patients with kidney impairment receiving bisphosphonates and chemotherapy.

Patients who develop MBD place a greater burden on health care systems than those who have cancer alone, and this burden further increases in those who subsequently develop an SRE.[9] Biosimilars are usually cheaper than their reference products and thus have potential to broaden access to key drugs.[10] The development of MW032 could further decrease the disease and economic burden for patients with advanced tumors. MW032 (coded name) is biosimilar to denosumab, which is a recombinant humanized anti-RANKL monoclonal antibody solution. A phase 1 study demonstrated that MW032 and denosumab were bioequivalent based on the similarity of their pharmacokinetics, pharmacodynamics, safety, and immunogenicity.[11] The aim of this study was to evaluate the biosimilarity in efficacy, safety, and population pharmacokinetics of MW032 and denosumab in patients with solid tumor bone metastases, based on a large-scale, 53-week, multicenter, phase 3 equivalence trial.

Key Points

Question Are the effects of a proposed denosumab biosimilar (MW032) equivalent to those of denosumab in the treatment of solid tumor–related bone metastases?

Findings In this randomized phase 3 equivalence trial that included 701 solid tumors from patients with bone metastasis, the end points evaluated by the bone turnover markers and the incidence of skeletal-related events were similar between MW032 and denosumab group. The 90% CI of the primary treatment outcome difference was within predefined equivalence margins.

Meaning MW032 and denosumab were biosimilar in efficacy, population pharmacokinetics, and safety profile; availability of denosumab biosimilars will broaden the access to denosumab and reduce the drug burden for patients with advanced tumors.

Methods

Participants

The key registration study was conducted in 46 clinical centers in China in accordance with the Technical Guidelines for Biosimilar Drug Development and Evaluation.[12] The trial protocol is avalable in Supplement 1. Eligible patients were aged 18 years or older with histologically confirmed malignant tumor (excluding blood cancer), radiographic evidence of at least 1 bone metastasis, adequate organ function with a life expectancy exceeding 6 months, and Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤2. A list of eligibility and exclusion criteria are provided in eTable 1 in Supplement 2). This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

The protocol was reviewed and approved by the relevant independent ethics committees at each center. All patients provided written informed consent before enrollment. This study was conducted in accordance with the terms of the Declaration of Helsinki, Good Clinical Practice guidelines, and all applicable regulatory requirements.

Study Design and Treatment

After confirmation of eligibility, patients were randomly assigned in a 1:1 ratio to MW032 or reference denosumab. Randomization was stratified by tumor type (breast cancer vs other cancers), SRE status (whether any SRE had occurred in the past).

Patients received 120 mg of MW032 or denosumab subcutaneously, every 4 weeks until week 49. Patients were advised to take daily supplements containing 500 mg of elemental calcium and at least 400 international units of vitamin D (cholecalciferol) during the study.

The incidence and severity of adverse events were assessed by investigators according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Analysis of urinary aminoterminal cross-linking telopeptide of type I collagen (uNTx) was performed using an enzyme-linked immunosorbent assay (ELISA) kit (SpectraMax340PC^{384} and VERSA max; Molecular Devices, Inc) at weeks 5, 9, 13, 25, 37, and 53, or at the end of treatment. Dose adjustment of investigational product was not permitted. Oral adverse events, hypocalcemia, and hypercalcemia were designated as events of interest based on the known safety profile of denosumab. SREs were monitored at each follow-up point during 53 weeks. Radiology assessment was performed

for all patients during the screening period, at 53 weeks, early withdrawal or following the opinions from investigators. Immunogenicity samples were collected within 1 hour before subcutaneous dosing of MW032 or denosumab on the first day, weeks 5, 13, 25, 37, and 53, or on early withdrawal from the study.

An interactive web response system was used by the funder to assign patients to study groups as per a predefined randomization code. Study participants, investigators, and study site personnel remained masked to randomization codes until all final clinical data had been entered into the database and the database had been locked and released for analysis.

Study End Points

The primary end point was percentage change in natural logarithmic transformed urinary N-telopeptide/creatinine ratio (uNTx/uCr) from baseline to week 13. Secondary end points were percentage change in uNTx/uCr and bone-specific alkaline phosphatase (s-BALP) from baseline to weeks 5, 25, 37, and 53, and the incidence of SREs.

Safety end points were the prevalence and severity of adverse events, and laboratory measures. Other safety end points were vital signs, electrocardiographic findings, chest radiographic findings, hypersensitivity monitoring, physical examination, and ECOG PS.

Statistical Analysis

The statistical analysis plan is available in Supplement 3. The efficacy analysis was based on natural logarithmic transformation of uNTx/uCr due to the nonnormal distribution. Sample size was determined by assuming that the mean (SD) difference between MW032 and denosumab was 0 (0.58), a 2-sided significance level $\alpha = 0.10$, a dropout rate of 10%, and power of 80%.

Clinical equivalence of the primary end point was demonstrated by comparing the 2-sided 90% CI of the mean difference of ln (uNTx/uCr) changes between MW032 and denosumab with the prespecified equivalence margin of −0.13 to 0.13,[13] which corresponds to a percentage change of between −68.8% and −76.2% for the biosimilar when the percent change from baseline for denosumab is −72.7%.

The least-square mean (LSM) difference and 90% CI were determined using the analysis of covariance (ANCOVA) model while adjusting for baseline uNTx/uCr and stratification factors (tumor type and SRE). The LSM difference, Δ, between ln (uNTx/uCr) at baseline and week 13 for each treatment group was calculated and back transformed to percentage change using the formula: change% = (exp (Δ) −1) ×100. The secondary efficacy end points s-BALP and uNTx/uCr for other time points were analyzed in the same way as for the primary end point.

For the exploratory end point of time to first on-study SREs was estimated by the Kaplan-Meier method and was compared between treatments by log-rank tests. Hazard rates (HRs) and 95% CIs were calculated from stratified Cox proportional hazards models adjusting for baseline uNTx/uCr and stratification factors (tumor type and SRE). Participants with deaths or other drop-out events were treated as censored cases.

Statistical analyses were performed using SAS (version 9.4; SAS Institute, Inc), Excel (version 365, Microsoft), and R (version 4.2.1, R Foundation).

Results

Patients

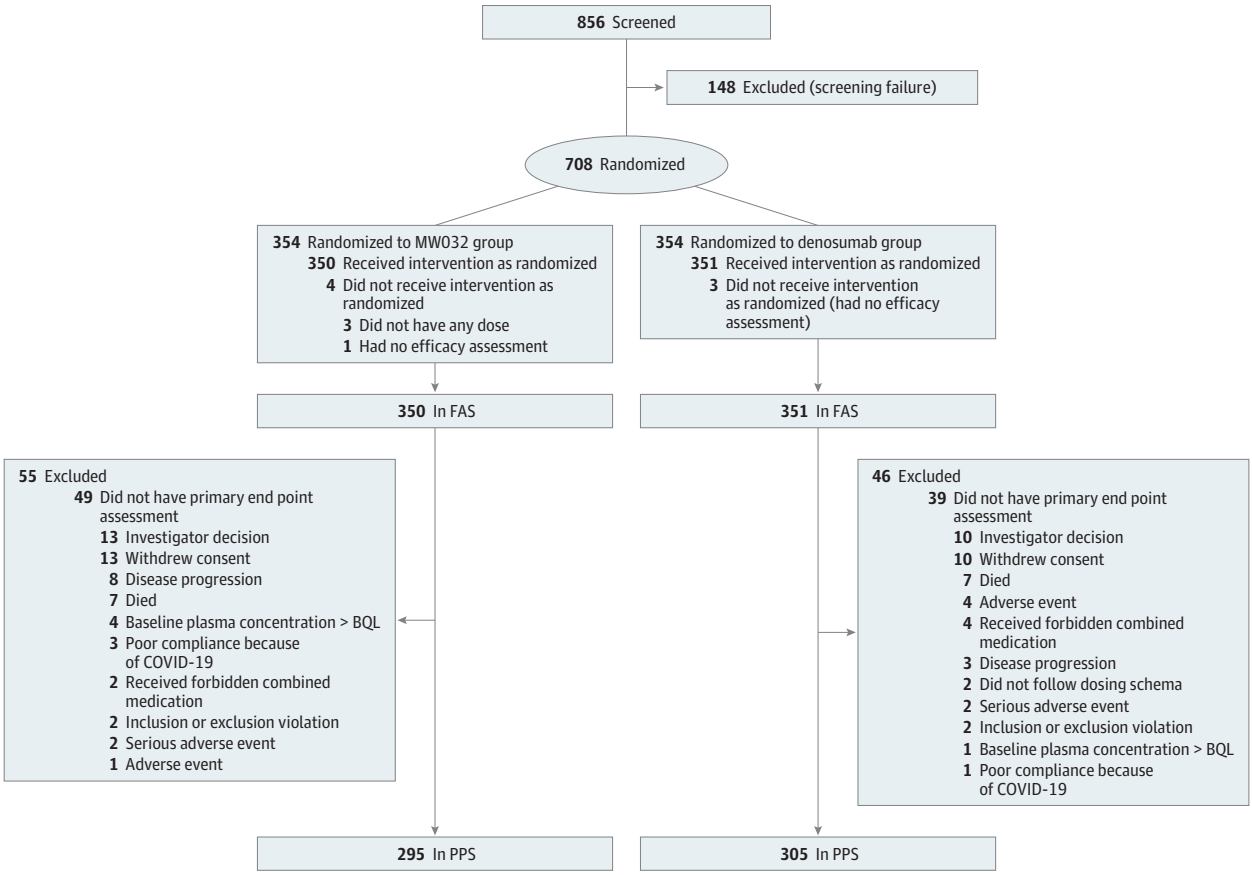
Between January 17, 2020, and April 30, 2021, 856 patients were screened and 708 patients were randomly allocated to receive either MW032 (n = 354) or denosumab (n = 354), from 46 clinical sites in China. The primary end point was assessable in 701 patients (n = 350, MW032; n = 351, denosumab). The probability proportional to size (PPS) population comprised 600 patients (n = 295, MW032; n = 305, denosumab). **Figure 1** shows details of the major protocol deviations that led to exclusion of patients from the PPS. Demographic and disease characteristics are reported based on the full analysis set (FAS) population, and the 2 treatment groups were well balanced (**Table 1**). Of the FAS population, the mean (range) age was 56.1 (22-86) years, 460 were women (65.6%), and breast cancer was the primary tumor in 331 patients (47.2%); SREs occurred prior to baseline in most patients (237 [67.7%] vs 236 [67.2%] in the MW032 and denosumab groups, respectively); baseline uNTx/uCr and s-BALP were similar in the 2 treatment groups.

Efficacy

According to FAS, the mean percent changes of 13-week uNTx/uCr from baseline were −72.0% and −72.7% in the MW032 group and the denosumab group, respectively, after adjusting for stratification factors (cancer type and previous SREs). These percent changes corresponded to mean ln-transformed uNTx/uCr of −1.27 and −1.30, or a difference of 0.02. The 90% CI for the difference (−0.04 to 0.09) was within the equivalence margin (−0.13 to 0.13). Sensitivity analysis was conducted by mixed model for repeated measures (MMRM), where the 90% CI (−0.04 to 0.09) of the 13-week difference of mean uNTx/uCr change from baseline also met predefined equivalence margins. The efficacy results from the PPS and the sensitivity analysis based on planned stratification were consistent with the FAS analysis. Considering the stratification factors, post hoc subgroup analysis also showed that the change of 13-week uNTx/uCr from baseline was not significantly different between the 2 treatment groups in breast cancer, lung cancer, or previous SRE subgroups (**Table 2**). For the secondary end points, the percentage change of the uNTx/uCr from baseline decreased sharply within 5 weeks and then remained at that level between weeks 5 and 53. There was no significant difference in the percentage change of uNTx/uCr between denosumab and MW032 groups at any time point during 53 weeks. The percentage change of s-BALP continued to decline until week 53, and the changes in the 2 treatment groups were not significantly different during 53 weeks of follow up (**Figure 2**; eFigure 1 in Supplement 2).

The incidence of SREs was also compared between the 2 groups during 53 weeks of follow up (eTable 2 in Supplement 2). SREs occurred in 32 patients in the MW032 group and 37 patients in the denosumab group. No statistical difference

Figure 1. Trial Profile



FAS indicates full analysis set; PPS, and BQL.

Table 1. Baseline Demographics and Characteristics

Characteristic	Total (n = 701)	MW032 (n = 350)	Denosumab (n = 351)
Age, mean (SD), y	56.1 (11.4)	55.9 (11.3)	56.3 (11.5)
Sex, No. (%)			
Male	241 (34.4)	125 (35.7)	116 (33.0)
Female	460 (65.6)	225 (64.3)	235 (67.0)
Race, No. (%)			
Chinese Han	663 (94.6)	330 (94.3)	333 (94.9)
Height, mean (SD), cm	162.01 (7.6)	162.11 (7.6)	161.9 (7.7)
Weight, mean (SD), kg	62.2 (11.2)	62.12 (11.1)	62.3 (11.2)
BMI index, mean (SD)	23.7 (3.7)	23.58 (3.6)	23.8 (3.8)
Location of primary tumor, No. (%)			
Breast	331 (47.2)	165 (47.1)	166 (47.3)
Lung	199 (28.4)	97 (27.7)	102 (29.1)
Other	171 (24.3)	88 (25.2)	83 (23.6)
Previous SRE, No. (%)			
SRE	473 (67.5)	237 (67.7)	236 (67.2)
No SRE	228 (32.5)	113 (32.3)	115 (32.8)
ECOG, No. (%)			
0	183 (26.1)	97 (27.6)	86 (24.3)
1	478 (68.2)	235 (67.0)	243 (68.6)
2	44 (6.3)	19 (5.4)	25 (7.1)
uNTx/uCr, mean (SD)	4.2 (0.8)	4.2 (0.8)	4.3 (0.8)
s-BALP, mean (SD)	2.9 (0.8)	3.0 (0.7)	2.9 (0.8)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ECOG, Eastern Cooperative Oncology Group; uNTX/uCr, natural logarithmic transformed urinary N-telopeptide/creatinine ratio; s-BALP, natural logarithmic transformed serum bone-specific alkaline phosphatase; SREs, skeletal-related events.

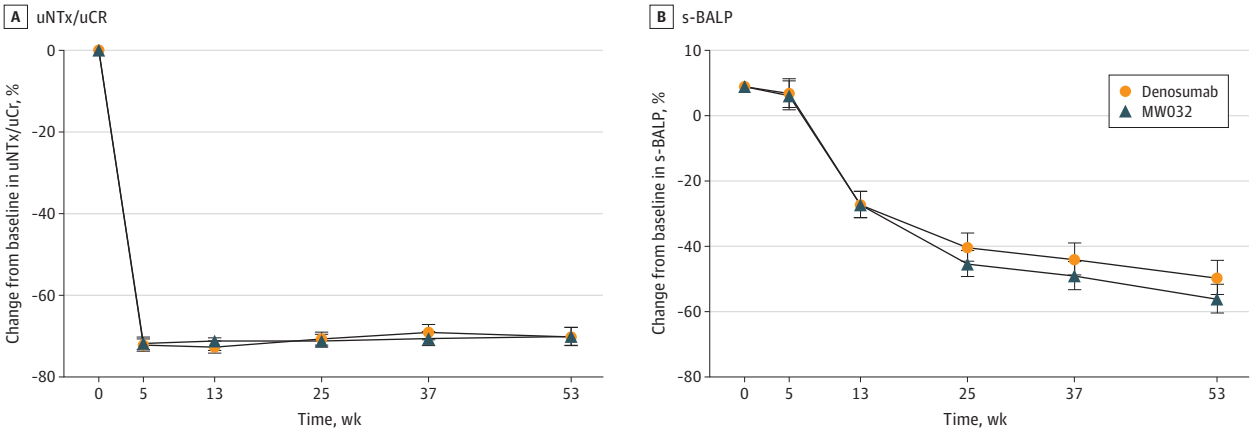
Table 2. Primary End Point and Subgroup Analysis[a]

Variable	Change from baseline, % (95% CI)		Least square mean change from baseline (95% CI)			
	MW032	Denosumab	MW032	Denosumab	Difference (90% CI)	*P* value
Primary end point						
FAS	−72.0 (−73.5 to −70.4)	−72.7 (−74.2 to −71.2)	−1.27 (−1.33 to −1.22)	−1.30 (−1.35 to −1.24)	0.02 (−0.04 to 0.09)	.50
FAS sensitivity	−71.1 (−72.7 to −69.5)	−71.9 (−73.4 to −70.3)	−1.24 (−1.30 to −1.19)	−1.27 (−1.32 to −1.21)	0.03 (−0.04 to 0.09)	.48
PPS	−71.4 (−73.0 to −70.0)	−72.2 (−73.7 to −70.7)	−1.25 (−1.31 to −1.20)	−1.282 (−1.34 to −1.23)	0.03 (−0.03 to 0.09)	.45
PPS sensitivity	−71.4 (−73.0 to −70.0)	−72.3 (−73.7 to −70.7)	−1.25 (−1.31 to −1.20)	−1.28 (−1.34 to −1.23)	0.03 (−0.03 to 0.09)	.44
Cancer subgroup						
Breast cancer	−70.6 (−72.8 to −68.2)	−72.5 (−74.6 to −70.2)	−1.22 (−1.30 to −1.15)	−1.29 (−1.37 to −1.21)	0.07 (−0.02 to 0.16)	.23
Lung cancer	−72.8 (−75.5 to −69.9)	−72.1 (−74.6 to −69.4)	−1.30 (−1.41 to −1.15)	−1.28 (−1.37 to −1.18)	−0.03 (−0.14 to 0.09)	.70
Other cancer	−71.7 (−74.9 to −68.1)	−71.7 (−75.0 to −67.9)	−1.26 (−1.38 to −1.14)	−1.26 (−1.39 to −1.14)	0.00 (−0.14 to 0.14)	>.99
Previous SRE subgroup	−71.7 (−73.6 to −69.7)	−73.8 (−75.5 to −72.0)	−1.26 (−1.33 to −1.19)	−1.34 (−1.41 to −1.27)	0.08 (−0.003 to 0.16)	.11

Abbreviations: FAS, full analysis set; PPS, probability proportional to size; SRE, skeletal-related events.

[a] Least square mean (LSM) change from baseline and the difference were determined using the analysis of covariance (ANCOVA) model while adjusting for baseline natural logarithmic transformed urinary N-telopeptide/creatinine ratio (uNTx/uCr) and stratification factors (tumor type and SRE). uNTx/uCr was calculated based on uNTx/uCr (nMBCE/mM) = uNTx (nM) / (uCr (mg/dL) × 0.0884). LSM was calculated based on the natural logarithmic transformed uNTx/uCr.

Figure 2. Mean Change From Baseline of Natural Logarithmic Transformed Urinary N-Telopeptide/Creatinine Ratio (uNTx/uCR) and Bone-Specific Alkaline Phosphatase (s-BALP) (Full Analysis Set Population)



The whiskers indicate the 95% CIs.

of SRE incidence was observed between the 2 groups (−1.4%; 95% CI, −5.8% to 3.0%). After adjusting for stratification factors, there was no statistically significant difference in the odds ratio between the 2 groups (0.8; 95% CI, 0.6-1.1).

In exploratory analyses (FAS and PPS population), we further evaluated the effect of MW032 and denosumab treatment on reduction of the HR for SREs (eFigure 2 in Supplement 2). No significant difference was found in reduction of hazard for SREs between the 2 groups in both FAS population (HR = 0.87; 95% CI, 0.54-1.39) and PPS population (HR = 0.77; 95% CI, 0.47-1.26). After adjustment for cancer type, previous SRE status and baseline uNTx/uCr, the risk reduction effect was also similar (adjusted HR, 0.87; *P* = .55 for FAS population).

Safety

Patients receiving at least 1 dose of investigational therapy (n = 705) were included in the safety analyses (351 patients in the MW032 group and 354 patients in the denosumab group). The proportion of patients reporting at least 1 treatment-emergent adverse event (TEAE) was similar between the 2 groups (**Table 3**). Outcomes of TEAEs were mostly improved, stabilized, or restored to baseline levels.

Treatment-related TEAEs with the highest incidence were hypocalcemia (125 MW032 [35.6%] vs 146 denosumab [41.2%]), hypophosphatemia (55 MW032 [15.7%] vs 38 denosumab [10.7%]) and hyperuricemia (24 MW032 [6.8%] vs 21 denosumab [5.9%]) in both treatment groups. Patients experiencing grade 3 or worse TEAEs were 189 (53.8%) in the

Table 3. Safety Analysis

Incidence of adverse events	No. (%) MW032 (n = 351)	Denosumab (n = 354)
TEAEs		
Total No. of TEAEs	341 (97.2)	342 (96.6)
Treatment-related	226 (64.4)	243 (68.6)
Grade 3 and above	189 (53.8)	204 (57.6)
Treatment-emergent SAEs	130 (37.0)	122 (34.5)
Treatment related	4 (1.1)	5 (1.4)
Treatment-related death	0	0
TEAEs leading to discontinuation	31 (8.8)	34 (9.6)
Withdraw due to TEAEs	4 (1.1)	11 (3.1)
TEAEs leading to deaths	41 (11.7)	27 (7.6)
Deaths from tumor progression	18 (5.1)	9 (2.5)
Deaths from CNS metastases	3 (0.9)	0
Deaths from meningeal metastases	1 (0.3)	0
Deaths from other causes	20 (5.7)	23 (6.5)
TEAEs of special interests		
Infectious adverse events	148 (42.2)	164 (46.3)
Treatment related	20 (5.7)	21 (5.9)
Abnormal liver function	15 (4.3)	18 (5.1)
Treatment related	1 (0.3)	2 (0.6)
Hypocalcemia	141 (40.2)	169 (47.7)
Treatment related	125 (35.6)	146 (41.2)
Adjudicated positive ONJ	1 (0.3)	0
Treatment related	1 (0.3)	0
Malignant disease progression	46 (13.1)	50 (14.1)
Treatment related	0	0
Kidney failure	3 (0.9)	6 (1.7)
Treatment related	1 (0.3)	1 (0.3)
Increased blood creatinine	19 (5.4)	29 (8.2)
Treatment related	8 (2.3)	10 (2.8)
Treatment-related TEAEs reported in 5% of either group		
Hypophosphatemia	55 (15.7)	38 (10.7)
Weakness	27 (7.7)	34 (9.6)
Hyperuricemia	24 (6.8)	21 (5.9)
Anemia	20 (5.7)	26 (7.3)
Back pain	12 (3.4)	18 (5.1)
Hypertriglyceridemia	9 (2.6)	20 (5.6)
Arthralgia	6 (1.7)	19 (5.4)

Abbreviation: CNS, central nervous system; ONJ, osteonecrosis of the jaw; TEAEs, treatment-emergent adverse events.

MW032 group and 204 (57.6%) in the denosumab group, and no notable differences were observed in TEAEs of special interest. Osteonecrosis of the jaw (ONJ) occurred in only 1 patient (MW032 group). It is worth noting that the incidence of hypocalcemia and increased blood creatinine levels were lower in the MW032 group, and this difference became smaller and nonsignificant (hypocalcemia) when analyzing the treatment-related cases. Importantly, the incidence of TEAEs leading to deaths in the MW032 group was higher than that in the denosumab group and the incidences were 11.7% (n = 41) and 7.6% (n = 27), respectively. However, most deaths were due to tumor progression (MW032, 5.1% vs denosumab, 2.5%), and were therefore unrelated to the study drug. Deaths from other causes were also judged as treatment unrelated and similar between the 2 groups (MW032, 20 vs denosumab, 23). Antidrug antibody (ADA) and neutralizing antibody (NAb) have also been tested (eTable 3 in Supplement 2).

Population Pharmacokinetics Modeling

The geometric means of the pharmacokinetics parameters (Cmax, AUC 0-t and AUC 0-inf) and their 90% CIs were all within the equivalent interval (0.80-1.25) and the Cssmin values and 95% CIs from 3 methods were similar between the MW032 and denosumab groups (eTable 4 and eTable 5 in Supplement 2).

Discussion

This was a randomized, double-blind, active controlled, multicenter trial to investigate the equivalence of MW032 and denosumab in patients with solid tumor-related bone metastases. The trial achieved its primary end point by proving that MW032 had an equivalent effect on week 13 uNTx/uCR compared with denosumab. All assessable secondary end points were also similar between the 2 groups at the end of week 53. MW032 was well-tolerated and exhibited low immunogenicity, having a similar safety and ADA/neutralizing antibody (NAb) profile to that of denosumab. Population pharmacokinetics simulation and classic pharmacokinetics parameters also supported the exposure equivalence between MW032 and the reference drug in patients with cancer with bone metastasis.

Week 13 uNTx/uCR was used as the primary end point in this study. N-terminal telopeptide (NTx) is a bone osteolytic product of type 1 collagen released during bone resorption. A meta-analysis of 12 130 patients in 17 studies showed that reductions in uNTx/uCr after 13 weeks were associated with lower risk of SREs.[14] Elevated uNTx levels in patients with bone metastases are also predictive of cancer progression and death, and normalization of NTx excretion rates is associated with relief of symptoms and reduced incidence of SREs.[15,16] uNTx has been widely used in denosumab studies as a surrogate end point for SRE risk in patients with MBD, especially employed in pharmacokinetics/pharmacodynamics studies.[17-19] The results of the present study also indicated that the maximum suppressive effect of denosumab, along with MW032, was seen at first visit (week 5), and this effect was sustained until the end of week 53 with 120 mg every 4 weeks. This reduction trend is also consistent with other denosumab studies.[17,20] The present study also compared s-BALP reduction during 53 weeks. Changes of s-BALP levels were equivalent between the 2 groups at each analysis point, but different from those of uNTx/uCr. The different trend of uNTx/Cr and s-BALP further confirmed that osteolysis is more sensitive to denosumab and MW032,[2] which is consistent with the mechanism of RANK/RANKL inhibition in osteoclasts.

The superiority of denosumab to zoledronic acid for prevention of SREs was demonstrated in 3 pivotal phase 3 stud-

ies. The delays until first and subsequent on-study SREs were employed as the main end points. Overall, denosumab reduced the hazard rate for first on-study SRE by 17%, for multiple SREs by 18%, and increased median time to first on-study SRE by 8.2 months (from 19.5 to 27.7 months).[21] The hazard reduction effect was consistent in the studies of patients with breast cancer[22] and castrate-resistant prostate cancer[23] based on superiority test, and this effect was 16% in a study of advanced cancer (excluding breast and prostate cancer) or multiple myeloma based on noninferior tests.[19] The present study also showed equivalent incidence of SREs after treatment with MW032 and denosumab. Using the exploratory end point of first on-study SRE, the risk was also equivalent in Kaplan-Meier and multivariable analyses, after adjusting for cancer types, previous occurrence of SREs and baseline uNTx/uCR. However, the follow-up durations of the 3 pivotal studies were more than 2 years, and the median time to first on-study SRE was not achieved in the present study.

The equivalence margin was often set up based on the rules for noninferiority margin. According to rules from US Food and Drug Administration guidance[24,25] and Chinese regulation,[13] a margin for noninferiority trial preserves at least 50% efficacy from historical data. In this case, the noninferiority margin would be 50% of the upper 50% CI, for the treatment effect difference (vs control) from the result in pivotal study of denosumab in China, where the difference of the change in the logarithm transformed uNTx/uCr from baseline to week 13 between denosumab and zoledronic acid groups was −0.32 (95% CI, −0.44 to −0.19). Taking half of the upper limit of the 50% CI (−0.36 to −0.27) because the statistical margins and the symmetric margin for an equivalence trial is then 0.13.

The safety profile of MW032 was consistent with the adverse events pattern expected in target patients receiving denosumab. No significant differences were observed in the incidence of hypocalcemia or hypophosphatemia, which were identified as risk factors for denosumab treatment. The decreases of serum calcium and phosphorus were mild or asymptomatic in most patients. Osteonecrosis of the jaw occurred once (MW032 group), and the frequency was much lower in the present study than in other phase 3 denosumab studies. Since the occurrence of ONJ is correlated with denosumab treatment duration, further studies of MW032 may extend the duration of observation. Management of kidney function is necessary in patients with cancer using certain chemotherapies and other nephrotoxic agents. The frequency of kidney-related AEs was similar in both groups. MW032 is eliminated through nonspecific catabolism in cells of the reticuloendothelial system, similarly to denosumab,[26] and is not reliant on kidney function. MW032 provides a therapeutic option for patients with cancer with kidney insufficiency and those receiving nephrotoxic regimens.

Limitations

To our knowledge, this study was the first to investigate the bioequivalence of denosumab biosimilar in a 53-week, multicenter, large scale, and head-to-head trial. A limitation of our study is the absence of long-term first on-study SRE and overall survival data. Although the risk of first on-study SRE was compared, no group achieved the median time to first on-study SRE. Another limitation is that the primary end point of week 13 uNTx/uCR was a surrogate end point representing the SRE risk.

Conclusion

In conclusion, MW032 was bioequivalent with reference denosumab in efficacy, with similar safety profile and population pharmacokinetics. This study demonstrated that MW032 is a potential novel biosimilar of denosumab and an effective option for solid tumor patients with bone metastases.

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