Clinical meaningfulness of duloxetine's effect in Chinese patients with chronic pain due to osteoarthritis: post hoc analyses of a phase 3 randomized trial

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Purpose: To evaluate the analgesic effect of duloxetine in Chinese patients with osteoarthritis (OA) of the knee/hip at individual patient level and report the relationship between pain intensity reduction, overall improvement, and physical functioning.

Patients and methods: Post hoc analysis of 13-week, phase 3, parallel-group, randomized, placebo-controlled study of duloxetine in Chinese patients with OA pain. Patients were randomized (1:1, computer-generated, interactive web-response system) to duloxetine (60 mg once daily, n=202) or placebo (n=207). Patients, investigators, and study staff were blinded throughout the study. Duloxetine's efficacy was evaluated using the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) and the Osteoarthritis Research Society International and Outcome Measures in Rheumatology (OARSI-OMERACT) responder criteria. Analyses were conducted on all randomized patients with a baseline and at least one post-baseline observation.

Results: At study endpoint, the percentage of patients experiencing ≥30% pain intensity reduction (30% responders) was significantly higher in the duloxetine group than in the placebo group (63.4% vs 49.7%; P=0.008). The percentage of patients experiencing $\geq 50\%$ pain intensity reduction (50% responders) in the duloxetine group was numerically higher than in the placebo group (42.8% vs 34.5%; P=0.098). Most of the 30% and 50% responders to duloxetine treatment felt either "very much improved" or "much improved" on the Patient Global Impression-Improvement at endpoint. The 30% and 50% responders to duloxetine treatment also experienced greater improvements in the Western Ontario and McMaster Universities Osteoarthritis Index physical function scores at endpoint compared with non-responders. The overall percentage of OARSI-OMERACT responders was significantly higher in the duloxetine group vs the placebo group (70.1% vs 54.9%; *P*=0.003).

Conclusion: Based on IMMPACT and OARSI-OMERACT criteria, the analgesic effect of duloxetine was associated with clinically relevant benefits in Chinese patients with OA of the

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Keywords: Chinese, chronic pain, duloxetine, clinical meaningfulness, efficacy, osteoarthritis

Introduction

Chronic pain is a hallmark symptom of many musculoskeletal disorders, including osteoarthritis (OA), rheumatoid arthritis, and chronic low back pain. Despite the current availability of analgesic options, many patients with OA are refractory to existing

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analgesic treatments or achieve only partial pain relief.^{2,3} To help optimize the potential for effective pain management, accurate and reliable pain measurement is required.

In clinical trials of chronic pain interventions, change in pain intensity from baseline commonly serves as the primary efficacy endpoint. However, several studies have emphasized the importance of assessing more than just pain. This is because, in addition to the subjective symptom of pain, patients with chronic pain also have diminished physical, mental, and social functioning. Furthermore, evaluation of pain using traditional outcome measures, including the Brief Pain Inventory (BPI) or the visual analogue scale, provide a measure of magnitude of variation of group effects; that is, average pain ratings or average changes in pain scores. However, these outcome measures are inadequate for quantifying response to treatment at the individual patient level.

For clinically meaningful interpretation of response to therapy, new outcome measures have been developed to evaluate pain and function. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) has recommended a set of outcome domains to interpret clinical meaningfulness of treatment outcomes at the individual patient level in clinical trials investigating efficacy of chronic pain treatments. 10,11 These recommendations include a set of provisional benchmarks for interpreting the clinical importance of changes that occur within individuals in measures of pain, physical and mental functioning, and global improvement. "Moderate" and "substantial" clinically important improvement were defined, respectively, as ≥30% and ≥50% pain intensity reduction. In addition, for OA, the Osteoarthritis Research Society International (OARSI) Standing Committee for Clinical Trials Response Criteria Initiative and the Outcome Measures in Rheumatology (OMERACT) committee developed a set of standardized response criteria for pain, physical functioning, and patient global assessment to identify responders in clinical trials on chronic pain. 12 Together, the IMMPACT and OARSI-OMERACT measurements, which are now recommended secondary outcomes in chronic pain clinical trials, 13 provide complementary and meaningful data at the individual patient level to aid in the interpretation of results from these trials.

Selective serotonin and norepinephrine reuptake inhibitors (SNRIs) have a central analgesic effect via the potentiation of activity in the descending pain inhibitory pathways. ¹⁴ Duloxetine, a potent SNRI, has demonstrated efficacy in various chronic pain conditions, including OA, diabetic peripheral neuropathic pain, fibromyalgia, and chronic low back pain. ¹⁵ A previous randomized, double-blind, 13-week,

phase 3, placebo-controlled study explored the efficacy and safety of duloxetine (Cymbalta, Eli Lilly and Company, Indianapolis, IN, USA) in Chinese patients with chronic pain due to OA of the knee or hip. 16 The primary analysis showed that duloxetine treatment resulted in significant pain reduction on a group mean level, compared with placebo treatment, on the BPI 24-hour average pain rating (least-squares mean change from baseline to endpoint [SE], duloxetine: -2.23 [0.11]; placebo: -1.73 [0.11]; P=0.001; effect size 0.33). 16 The present post hoc analysis used the IMMPACT and the OARSI-OMERACT responder criteria to analyze the proportions of patients who reported clinically relevant changes in pain severity, physical functioning, and overall improvement. This post hoc analysis, with a focus on the analgesic effect of duloxetine at the individual patient level, was undertaken as a complementary analysis of the primary efficacy results.

Patients and methods Study design

This study was a post hoc analysis of a randomized, multicenter, double-blind, parallel, placebo-controlled, 13-week, phase 3 clinical trial comparing the efficacy and safety of duloxetine (60 mg, once daily) with placebo in Chinese patients with chronic pain due to OA of the knee or hip. 16 The study was conducted from December 2012 to June 2015 at 17 study sites in PR China, in accordance with consensus ethics principles derived from international ethics guidelines, International Conference on Harmonization Good Clinical Practices E6, and all applicable laws and regulations. The study protocol and informed consent were approved by each site's ethics review board (Table S1). Written informed consent was obtained from each patient before participation. This trial is registered with ClinicalTrials.gov (NCT01931475). Details on the study design, eligibility criteria, and findings from the primary analysis have been published previously. 16

Patients who met the eligibility criteria were randomly assigned (1:1) to receive once-daily oral doses of duloxetine 60 mg or placebo. Duloxetine was started at 30 mg for 1 week and then titrated up to duloxetine 60 mg during the 13-week treatment phase. Randomization of patients was determined by a computer-generated random sequence using an interactive web-response system and was stratified by site with the block size of 4. Study drugs were indistinguishable, and all patients took the same number of capsules. Patients, investigators, and study personnel were blinded to treatment assignments until the end of the study, except the study statistician, who was unblinded to each patient's treatment assignment after completion of the double-blind treatment phase.

Study population

Male and female outpatients ≥40 years of age who met clinical and radiographic criteria defined by the American College of Rheumatology^{17,18} for the diagnosis of OA of the knee or hip with symptoms, including pain for ≥14 days of each month for 3 months before study entry, were eligible for inclusion. A BPI 24-hour average pain (ranging from 0 for no pain to 10 for worst pain imaginable) rating of ≥4 at screening was required. Patients diagnosed with psychiatric disorders, taking any excluded medications (analgesic agents including nonsteroidal anti-inflammatory drugs, acetaminophen/paracetamol, and opioids) that could not be discontinued at the first study visit, and patients anticipated by the investigator to require excluded medications during the study were excluded.

Outcome measures

The primary and secondary efficacy measures (BPI 24-hour average pain rating, BPI-Severity, BPI-Interference, Patient Global Impression of Improvement [PGI-I], the Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC], and the Clinical Global Impression of Severity) and safety measures were reported in the primary publication.¹⁶

In this post hoc analysis, the time course of changes in proportions of patients with $\geq 30\%$ pain intensity reduction and $\geq 50\%$ pain intensity reduction over the 13-week treatment period with duloxetine and placebo was reported.

Duloxetine's efficacy assessed using the IMMPACT responder criteria included domains of pain severity, patient ratings of overall improvement, and physical functioning. A responder was defined as a patient with a specified improvement in pain level, defined as ≥30% pain intensity reduction (moderately clinically important improvement) or ≥50% pain intensity reduction (substantial clinically important improvement) from baseline in the BPI 24-hour average pain rating. 10 To further assess whether pain reduction is related to improvement in physical function, the mean change in the WOMAC physical function score from baseline to endpoint was analyzed by response status of BPI average pain in the duloxetine group. The relationship between pain intensity reduction and overall improvement on the PGI-I scale at endpoint was also analyzed in the duloxetine group. Changes of "much improved" (PGI-I at endpoint =2) and "very much improved" (PGI-I at endpoint =1) were considered "moderately" to "substantially" important, respectively.

Duloxetine's efficacy assessed using the modified OARSI-OMERACT criteria¹² included modifications made for a 0- to 10-point scale (vs a 0- to 100-point scale) and data collection using the PGI-I (vs PGI-Severity). A responder was defined as a patient with: 1) \geq 50% pain intensity reduction and \geq 2 points decrease from baseline in the BPI average pain rating; or 2) \geq 50% reduction from baseline and \geq 13.6 points decrease in WOMAC physical function score; or 3) meeting at least two of the following three conditions: 1) \geq 20% pain intensity reduction and \geq 1 point absolute reduction from baseline in the BPI average pain rating; 2) \geq 20% reduction and \geq 6.8 point absolute reduction in WOMAC physical function score; or 3) PGI-I \leq 2 at endpoint.

Statistical analysis

A sample size of 200 patients per group was calculated to provide 90% statistical power to detect a between-group difference in the change in BPI 24-hour average pain rating (primary outcome of the trial, reported previously)¹⁶ of 0.73 points (SD of 2.2), assuming discontinuation rate of 4%. For the imputation of missing data, a baseline carried forward approach was used for the analysis of time course of response (ie, \geq 30% and \geq 50% pain intensity reduction) and a last observation carried forward approach for all other analyses. Analyses included all randomized patients with a baseline and at least one post-baseline observation.

Fisher's exact test was applied for comparing the response rate between duloxetine and placebo at each visit time point. The Jonckheere-Terpstra test was applied to test whether the percent changes in 24-hour average pain were the same across different PGI-I ratings at endpoint (null hypothesis). This test was performed within each treatment group separately, and also on the whole population with the two treatment groups combined. For the IMMPACT and OARSI-OMERACT responder analysis, Fisher's exact test was applied to compare responder proportions between duloxetine and placebo, and the number needed to treat (NNT) (that is, the number of patients needed to be treated with duloxetine for one additional patient to respond compared with placebo) was calculated as the reciprocal of the absolute risk reduction.¹⁹ Treatment effects were evaluated based on two-sided tests with a significance level of 0.05. Analyses were conducted with SAS Version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline clinical characteristics

Of 481 patients who entered the study, 407 patients were randomized to receive either duloxetine (n=205) or placebo (n=202). Most patients were female (76.4%), the mean age was 60.5 years, and mean duration of pain due to OA was

7.99 years. ¹⁶ Baseline pain severity and function assessments were similar between the two treatment arms. The mean (SD) baseline BPI 24-hour average pain was 5.4 (1.23), PGI-Severity was 4.2 (1.02), and functional impairment measured by the WOMAC physical function subscale was 26.7 (10.39).

Time course of response rate

Over 13 weeks, the proportion of patients experiencing $\geq 30\%$ and $\geq 50\%$ pain intensity reduction was consistently higher with duloxetine compared with placebo. The difference between the proportions of patients in the duloxetine group and placebo group with $\geq 30\%$ pain intensity reduction was

observed as early as Week 1 of treatment; this proportion increased over time and reached 59.8% with duloxetine and 47.7% with placebo by Week 13 (P=0.020; Figure 1A). Similarly, the proportion of patients with \geq 50% pain intensity reduction increased over time and reached 40.2% with duloxetine and 33.0% with placebo by Week 13 (P=0.143; Figure 1B).

IMMPACT responder criteria

Pain severity

As previously published,¹⁶ the individual patient responder analyses based on the BPI 24-hour average pain severity rat-

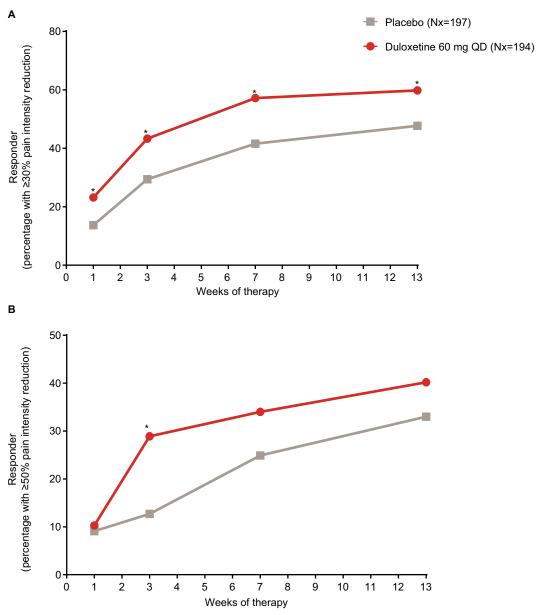


Figure I Time course of response rate, all randomized patients.

Notes: Percentage of patients achieving at least 30% pain intensity reduction (**A**) and percentage of patients achieving at least 50% pain intensity reduction (**B**). *P<0.05 comparing duloxetine with placebo.

Abbreviations: Nx, number of all randomized patients with non-missing data at baseline and endpoint (baseline observation carried forward); QD, once daily.

ing showed that the proportion of patients who experienced \geq 30% pain intensity reduction was significantly higher in the duloxetine group compared with the placebo group (63.4% vs 49.7%; P=0.008, NNT=8). The proportion of patients who experienced \geq 50% pain intensity reduction was numerically higher in the duloxetine group compared with the placebo group (42.8% vs 34.5%; P=0.098, NNT=13).

Association between pain intensity reduction and overall improvement

An analysis of the relationship between pain intensity reduction and overall improvement at endpoint (as measured by PGI-I) was conducted in patients in the duloxetine group (Figure 2A). Among patients who experienced ≥30% pain intensity reduction, 4.9% felt "very much improved" and 47.2% felt "much improved". Among the non-responders,

42.3% felt "minimally improved" and 42.3% felt "no change or worse". Similar results were observed in patients who experienced \geq 50% pain intensity reduction. The reduction from baseline in BPI average pain increased with the level of improvement in PGI-I rating at endpoint in both the duloxetine and placebo groups (P<0.001 for both the duloxetine group and the placebo group for the association between change in BPI average pain and PGI-I rating at endpoint) (Figure 2B).

Association between pain intensity reduction and physical functioning

An analysis of the relationship between pain intensity reduction and improvement in WOMAC physical function score was conducted in patients in the duloxetine group. Patients who experienced ≥30% pain intensity reduction

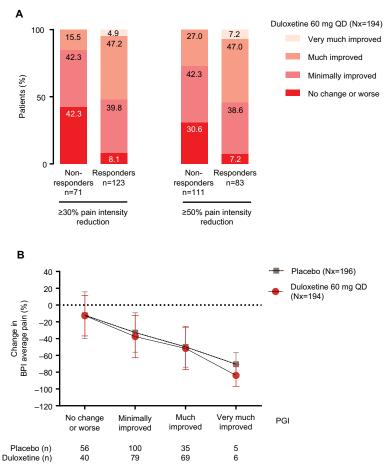


Figure 2 Relationship between BPI and PGI: association between pain intensity reduction and overall functional improvement at study endpoint (last observation carried forward).

Notes: The percentages of patients in different PGI-I categories were computed for patients experiencing <30% and ≥30% pain intensity reductions, and for patients experiencing <50% and ≥50% pain intensity reductions in the 24-hour BPI average pain, duloxetine group patients (**A**). Percent changes in the 24-hour BPI average pain compared with PGI-I assessment recorded at study endpoint, all randomized patients (**B**). Error bars represent SDs.

Abbreviations: n, number of patients in the indicated category; BPI, Brief Pain Inventory; Nx, number of all randomized patients with non-missing data at baseline and endpoint (last observation carried forward); PGI-I, Patient Global Impression of Improvement; QD, once daily.

had significantly greater improvement in physical functioning at endpoint compared with non-responders (mean [SD] -12.23 [8.65] vs -5.36 [8.75], P<0.001; Figure 3). Similarly, patients who experienced $\geq 50\%$ pain intensity reduction had a significantly greater improvement in physical functioning compared with non-responders (mean [SD] -13.43 [8.57] vs -7.08 [8.86], P<0.001).

Modified OARSI-OMERACT responder criteria

By 13 weeks, the proportion of patients with a clinical response according to the modified OARSI-OMERACT

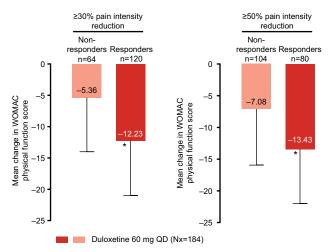


Figure 3 Improvements in WOMAC physical function from baseline to endpoint by categorical response status of pain reduction, duloxetine group patients.

Notes: *P<0.001 comparing responders with non-responders (for both ≤30% pain intensity reduction and ≤50% pain intensity reduction). Error bars represent SDs.

Abbreviations: n, number of patients in the indicated category; Nx, number of all randomized patients with non-missing data at baseline and endpoint (last observation carried forward); WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; QD, once daily.

response criteria was significantly higher in the duloxetine group than in the placebo group (*P*=0.003, NNT=7; Table 1).

Discussion

Both IMMPACT and OARSI-OMERACT responder criteria recognize the multidimensional nature of pain and have recommended key outcome measures that incorporate pain, physical functioning, and global improvement. 10-12 To our knowledge, this is the first study to use both the IMMPACT and the OARSI-OMERACT responder criteria to assess the efficacy of duloxetine at the individual patient level using data from a single randomized study of Chinese patients with OA of the knee or hip. The present analysis demonstrated that the benefit of duloxetine compared with placebo in Chinese patients with OA was clinically relevant and consistent across both responder criteria. A greater proportion of patients in the duloxetine group compared with those in the placebo group responded to treatment in terms of pain intensity reductions. In addition to a rapid onset of pain intensity reduction, treatment with duloxetine was associated with improvements in outcomes of physical functioning and overall improvement. Given the recent recommendations on assessment of physical function in chronic pain clinical trials, 13 our findings on the analgesic effect of duloxetine may help clinicians treating patients with OA pain.

There was a steady increase in the proportion of patients who experienced $\geq 30\%$ and/or $\geq 50\%$ pain intensity reduction throughout the 13-week treatment period. In addition, the time course of response rate demonstrated an early divergence in patients who experienced $\geq 30\%$ pain intensity reduction between Week 1 and Week 3 in favor of duloxetine over placebo. This is consistent with results from a study that reviewed 12 double-blind, placebo-controlled trials of dulox-

Table I Modified OARSI-OMERACT responder analysis

Variable, n (%)	Duloxetine (N=205) (Nx=184) ^a	Placebo (N=202) (Nx=182) ^a	Total (N=407) (Nx=366) ^a	<i>P</i> -value ^b
Overall response	129 (70.1)	100 (54.9)	229 (62.6)	0.003
BPI average pain with ≥50% reduction and ≥2 points decrease	80 (43.5)	65 (35.7)	145 (39.6)	0.136
WOMAC physical function score with ≥50% reduction and	47 (25.5)	29 (15.9)	76 (20.8)	0.028
≥13.6 points decrease				
Met at least two of the following three conditions:	114 (62.0)	85 (46.7)	199 (54.4)	0.005
BPI average pain with ≥20% reduction and ≥1 point decrease	142 (77.2)	121 (66.5)	263 (71.9)	0.027
WOMAC physical function score with ≥20% reduction and	112 (60.9)	91 (50.0)	203 (55.5)	0.046
≥6.8 points decrease				
PGI-I ≤2 at endpoint	74 (40.2)	37 (20.3)	111 (30.3)	<0.001

Notes: ^aPercentages are based on N and Nx in each column; ^bFrequencies were analyzed using a Fisher's exact test.

Abbreviations: OMERACT, Outcome Measures in Rheumatology; OARSI, Osteoarthritis Research Society International; Nx, number of all randomized patients with non-missing data at baseline and endpoint (baseline observation carried forward); BPI, Brief Pain Inventory; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; PGI-I, Patient Global Impression of Improvement.

etine (60–120 mg/day) in patients with chronic pain due to OA, diabetic peripheral neuropathic pain, fibromyalgia, and chronic low back pain, in which patients receiving duloxetine experienced a \geq 30% average pain intensity reduction as early as Weeks 1–3 of treatment.²⁰

Responder analyses make it possible to compare percentages of patients experiencing clinically meaningful outcomes in a readily interpretable manner. 21 According to IMMPACT, clinical meaningfulness can be assessed using the results of a responder analysis, specifically, ≥30% pain intensity reduction (for "moderately clinically important" change) or ≥50% pain intensity reduction (for "substantial clinically important" change). 10 Consistent with these definitions, the present study showed that a greater proportion of patients in the duloxetine group experienced moderate or substantial clinically important improvements in pain intensity compared with patients in the placebo group, thus demonstrating clinically relevant pain reduction with duloxetine.16 These results are similar to those from a previously reported 13-week, double-blind, randomized, placebo-controlled study of duloxetine for treatment of patients (n=231) with OA knee pain. The study reported a statistically significant moderate improvement in pain intensity in 59.3% of patients receiving duloxetine compared with 44.5% of patients receiving placebo (P=0.033).²² Similarly, a statistically significant substantial improvement in pain intensity was reported in 47.2% of patients receiving duloxetine compared with 29.4% of patients receiving placebo (P=0.006).22

Studies have shown that successful treatment of chronic pain is strongly associated with an improvement in physical functioning, which in turn leads to a perception of overall improvement.^{5,23} The primary analysis of the current study demonstrated that treatment with duloxetine vs placebo in Chinese patients with OA of the knee or hip resulted in significantly greater improvements in physical functioning as well as overall improvement. ¹⁶ Further analysis in the present study showed that responders in the duloxetine group reported clinically important improvements in physical functioning as reflected by the WOMAC function score. Also, most responders in the duloxetine group reported PGI-I ratings of "very much improved" or "much improved" at the end of the study. These results imply that patients in the duloxetine group who experienced either moderate or substantial pain intensity reduction compared with non-responders were more likely to achieve benefits in physical functioning and overall improvement.

In the present analysis, overall modified OARSI-OMERACT response rates were significantly greater in the duloxetine group compared with the placebo group. These results are consistent with those from a pooled analysis of two 13-week, double-blind, randomized, placebo-controlled trials comparing duloxetine 60-120 mg/day with placebo in patients with symptomatic OA of the knee,²⁴ and with a double-blind, randomized, placebo-controlled trial comparing duloxetine 60 mg/day with placebo in Japanese patients with knee pain due to OA.²⁵ In the pooled trials, patients receiving duloxetine were 33% more likely to achieve an OARSI-OMERACT response compared with patients on placebo (P<0.001, NNT=6), and in the Japanese trial OARSI-OMERACT response was significantly greater for duloxetine compared with placebo (adjusted risk ratio 1.35, P<0.0001).

The results of this study are strengthened by the fact that data are from a well-conducted randomized, double-blind trial, with sufficient sample size to reduce bias. Further, the present analysis was designed within the context of IMMPACT and OARSI-OMERACT recommendations, which are validated instruments for measuring clinically important outcomes in clinical trials of chronic pain. Clearly, our study is limited by the fact that the present analysis was not predefined. However, the present results were consistent across both responder criteria used. These findings should be confirmed in a prospective randomized controlled study in patients with chronic pain due to OA. Yet another limitation is the length of the trial; longer-term trials, such as the one conducted in Japan,²⁶ are required to fully assess the analgesic efficacy of duloxetine that is more reflective of clinical practice.

Conclusion

The findings of our study strongly support the efficacy of duloxetine for the treatment of pain in Chinese patients with symptomatic OA of the knee or hip. Specifically, the analgesic effect of duloxetine was associated with benefits in physical functioning and patients' ratings of overall improvement in this patient population. Addition of duloxetine, a centrally acting analgesic, to the present array of analgesic treatments for Chinese patients with OA could benefit patients with suboptimal/refractory responses to other available treatment options, especially patients with a central sensitization component to their chronic pain. Our results also suggest that the IMMPACT and/or OARSI-OMERACT responder criteria may be beneficial in determining a clinical response at an individual patient level, offering the opportunity to evaluate analgesic effect from a new angle in clinical practice.

Yue et al Dovepress

Data sharing statement

Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request in a timely fashion after the indication studied has been approved in the US and EU and after primary publication acceptance. No expiration date of data requests is currently set once they are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment for up to 2 years per proposal. For details on submitting a request, see the instructions provided at www.clinicalstudydatarequest.com.

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Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

Eli Lilly and Company was involved in the study design, data collection, data analysis, and preparation of the manuscript. YW and C-NW are employees of Lilly Suzhou Pharmaceutical Co. Ltd. LY is a former employee of Lilly Suzhou Pharmaceutical Co. Ltd.; work on the manuscript was completed during tenure as a Lilly employee. VS is an employee of Eli Lilly and Company. HD is an employee of Eli Lilly de Mexico. LY and HD have stock/equity ownership in Eli Lilly and Company. SL has nothing to declare. The authors report no other conflicts of interest in this work.

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Supplementary material

Table SI Ethics Review Boards

Ethics Review Boards (ERBs) and Ethics Committees	Location	
ERB of China-Japan Friendship Hospital	Beijing, PR China	
Ethics Committee of Guanghua Hospital	Shanghai, PR China	
ERB of the Third Xiangya Hospital of Central South University	Changsha, Hunan, PR China	
ERB of Anhui Provincial Hospital	Hefei, Anhui, PR China	
Shanghai Changhai Hospital Ethics Committee	Shanghai, PR China	
ERB of Jilin University China-Japan Union Hospital	Changchun, Jilin, PR China	
Clinical Medical Ethics Committee of the First Affiliated Hospital of Bengbu Medical College	Bengbu, Anhui, PR China	
ERB of the Second Xiangya Hospital of Central South University	Changsha, Hunan, PR China	
ERB of the First Affiliated Hospital of Anhui Medical University	Hefei, Anhui, PR China	
ERB of Tianjin Medical University General Hospital	Tianjin, PR China	
ERB of West China Hospital of Sichuan University	Chengdu, Sichuan, PR China	
ERB of the General Hospital of Shenyang Military Region	Shenyang, Liaoning, PR China	
ERB of the First Affiliated Hospital of Jinan University	Guangzhou, Guangdong, PR China	
ERB of Nanfang Hospital	Guangzhou, Guangdong, PR China	
ERB of Pingxiang People's Hospital	Pingxiang, Jiangxi, PR China	
ERB of Zhuzhou Central Hospital	Zhuzhou, Hunan, PR China	

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