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Efficacy and safety of duloxetine in Chinese patients with chronic pain due to osteoarthritis: A randomized, double-blind, placebo-controlled study

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Running title: Duloxetine for osteoarthritis pain
Abstract

**Objective:** We assessed the efficacy and safety of duloxetine (60 mg, once daily), compared with placebo, during a 13-week treatment period in Chinese patients with chronic pain due to osteoarthritis (OA).

**Design:** Patients were at least 40 years old (male or female) who met American College of Rheumatology clinical and radiographic criteria for the diagnosis of OA of the knee or hip. The primary efficacy measure in this phase 3, randomized, double-blind, placebo-controlled clinical trial was assessment of pain severity by the Brief Pain Inventory (BPI) 24-hour Average Pain rating. The clinical trial was conducted at 17 study centers. Statistical approaches included mixed-effects model repeated measures and analysis of covariance. A Fisher exact test was applied to categorical variables.

**Results:** Of 407 patients randomized (duloxetine: N=205; placebo: N=202), 166 (81.0%) patients from the duloxetine group and 176 (87.1%) patients from the placebo group completed the 13-week treatment phase. The majority (76.4%) of patients were female; mean age was 60.5 years. Duloxetine-treated patients reported significant pain reduction, compared with placebo treatment, on the BPI 24-hour Average Pain rating (least-squares mean change from baseline to endpoint [95% confidence interval], duloxetine: -2.23; placebo: -1.73; difference=-0.50 [-0.80, -0.20]; p=0.001). The incidence of discontinuations due to adverse events was 9.0% in duloxetine-treated patients and 4.5% in placebo-treated patients (p=0.109).

**Conclusions:** This study demonstrated the efficacy of duloxetine in Chinese patients with chronic pain due to OA. The safety profile of duloxetine observed in this study was consistent with that in previous duloxetine trials.

This trial is registered with ClinicalTrials.gov (NCT01931475).
Key Words: duloxetine, osteoarthritis, chronic pain, treatment, Chinese
Introduction

Osteoarthritis (OA) is a disease of the joints that results from breakdown of cartilage and underlying bone, most commonly in the knee, hip, and hand. The most common symptoms of OA are joint pain, loss of function, and stiffness\(^1\). The worldwide prevalence of OA is estimated to be 9.6% for men and 18.0% for women \(\geq 60\) years old\(^2\). OA is also common in China. A survey in Beijing found that OA of the knee affects 5.6% of men and 15% of women \(\geq 60\) years of age\(^3\). Another survey, in Guangzhou, found that OA of the knee affects 9.1% of men and 20.5% of women \(\geq 40\) years of age\(^4\).

Analgesics commonly used to treat OA pain in China include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), weak opioids (such as, oral codeine and tramadol), and topical capsaicin\(^5\). However, these drugs have limited efficacy and/or are associated with safety concerns\(^6\). Therefore, other treatment options are needed.

Recently, it has been shown that augmented central pain processing may play a role in peripheral or nociceptive pain conditions, such as OA\(^7\). Impaired activity of descending inhibitory pain pathways may contribute to certain chronic pain states\(^8\)\(^\)\(^-\)\(^10\). Indeed, activation of descending pain pathways by aerobic exercise, for example, has proven benefits\(^11\).

The neurotransmitters serotonin and norepinephrine are involved in these descending inhibitory pathways\(^12\)\(^\)\(^\)\(^,\)\(^13\). Duloxetine is a potent and selective inhibitor of serotonin and norepinephrine reuptake in the central nervous system in vitro and in vivo\(^14\). In addition, duloxetine has been approved for the treatment of diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain in the United States as well as in other countries. Given the similar pharmacokinetic profiles of duloxetine between Chinese and Caucasians\(^15\)\(^\)\(^,\)\(^16\), it is thought that duloxetine may also prove effective in the treatment of chronic pain in Chinese patients. Indeed,
duloxetine has shown efficacy in treating diabetic peripheral neuropathic pain in Chinese patients\textsuperscript{17}.

The primary objective of this 13-week study was to assess the efficacy of duloxetine (60 mg, once daily [QD]), compared with placebo, in the reduction of OA-related knee or hip pain severity in Chinese patients, as measured by the Brief Pain Inventory (BPI) 24-hour Average Pain rating. Secondary objectives included further assessments of the reduction of OA-related pain over the 13-week treatment period and the evaluation of the safety and of health outcomes in this population.

**Methods**

This was a multicenter, randomized, phase 3, double-blind, parallel clinical trial, comparing the efficacy and safety of duloxetine 60 mg QD with placebo in Chinese patients with OA knee or hip pain during a 13-week treatment period, followed by a 13-week open-label treatment period. This study was conducted from December 2012 to June 2015 at 17 study centers in China. This manuscript will only present the results of the 13-week double-blind treatment period.

**Patients**

This study included male and female outpatients of at least 40 years of age who met clinical and radiographic criteria for the diagnosis of OA of the knee or hip, had pain for ≥14 days of each month for 3 months prior to study entry, and had a rating ≥4 on the BPI 24-hour Average Pain item (Question 3 of the BPI-modified short-form) during screening, prior to treatment.

Patients were excluded from the study if they had any diagnosis of psychosis, bipolar disorder, schizoaffective disorder, current major depressive disorder, anxiety disorders (excluding
phobias), alcohol or eating disorders, or suicidal risk. Also excluded were patients who were taking any excluded medications (analgesic agents including but not limited to NSAIDs, acetaminophen/paracetamol, and opioids) that could not be discontinued at the first study visit and patients who were anticipated by the investigator to require use of excluded medications during the study. After the start of treatment, episodic use of short-acting analgesics was allowed for management of breakthrough OA knee/hip pain (rescue therapy) or unrelated acute conditions. “Episodic use” was defined as no more than 3 consecutive days, not exceeding 20 total days. No rescue medication was allowed during the 24 hours prior to any study visit.

**Disease diagnostic criteria**

The American College of Rheumatology criteria for diagnosis of OA were used. For the knee, OA disease criteria included knee pain, osteophytes (with radiographic evidence), and at least one of the following three conditions: age >50, morning stiffness <30 minutes, or crepitus.

For the hip, OA disease criteria included hip pain and at least two of the following three conditions: erythrocyte sedimentation rate <20 mm/h, femoral or acetabular osteophytes (with radiographic evidence), or radiographic joint space narrowing (superior, axial and/or medial).

The presence of osteophytes in the index knee or hip and the hip joint space narrowing were confirmed by historical record of imaging studies (any of the following: plain x-ray, computed tomography [CT], or magnetic resonance imaging [MRI] within the last 2 years). In cases with no history of relevant imaging studies, an x-ray of the index knee or hip taken during the screening period was used instead.

**Study design**

This multicenter, randomized, parallel, placebo-controlled clinical trial included five study periods: a 1-week screening phase (Study Period I), a 13-week double-blind treatment phase
(Study Period II), a 1-week titration phase (Study Period III), a 12-week open-label treatment phase (Study Period IV), and a 1-week taper phase (Study Period V). Only results of the 13-week double-blind treatment phase are being presented in this communication. Patients who met enrollment criteria during Study Period I continued into Study Period II and were randomized in a 1:1 ratio to either duloxetine 60 mg or placebo. Assignment to treatment groups was determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS was used to assign investigational product packages to each patient throughout this study. To achieve between-group comparability for site factor, randomization was stratified by site with the block size of four. Emergency codes, generated by a computer drug-labeling system, were available to the principal investigator.

Patients, investigators, and all other personnel involved in the conduct of the study were blinded to individual treatment assignments during the double-blind treatment phase. After all patients completed or discontinued from the double-blind treatment phase, a reporting database was validated and locked to analyze the data from this phase. At this point, each patient’s treatment assignment during Study Period II was unblinded to the statisticians (patients’ treatment assignment was kept blinded to patients, investigators, and physicians until the end of the study). All study drugs used were identical in color, shape, smell, and taste, and all patients took the same number of capsules regardless of their treatment group assignment.

Patients assigned to duloxetine were started on duloxetine 30 mg for 1 week and then titrated up to duloxetine 60 mg. Patients who could not tolerate duloxetine 60 mg QD during the treatment phase were discontinued from the study and entered Study Period V (Taper Phase) to minimize discontinuation-emergent adverse events, with the following exceptions: patients discontinued due to suicide risk; patients who do not require tapering of study drug in the clinical opinion of the treating physician; and patients who discontinued at or before dose escalation.
Ethical considerations

The study was conducted in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, the Council for International Organizations of Medical Sciences International Ethical Guidelines, the International Conference on Harmonisation Good Clinical Practice Guideline [E6], and all applicable laws and regulations. The ethics review boards (ERBs) and ethics committees that approved the protocol for this study are listed in Supplemental Table 1. Written informed consent was obtained from all patients before participation in the study. This trial is registered with ClinicalTrials.gov (NCT01931475).

Outcome measures

All scales were translated into Chinese, and the translation was validated (but the Chinese version of the scale itself was not revalidated). The primary efficacy measure was the reduction of pain severity, as measured using the BPI 24-hour Average Pain rating. The BPI is a self-reported scale that measures the severity of pain and the interference of pain on function20. In addition to Average Pain, the BPI-Severity items include Worst Pain, Least Pain, and Pain Right Now. The severity items ratings range from 0 (no pain) to 10 (pain as severe as one can imagine). The BPI-Interference items ratings range from 0 (does not interfere) to 10 (completely interferes). Two definitions for response to treatment were used: ≥30% and ≥50% reduction from baseline in the BPI 24-hour Average Pain severity ratings. Other measures included the Patient Global Impression of Improvement (PGI-Improvement)21, the Western Ontario and McMaster Universities Arthritis Index (WOMAC) Physical Function, Pain, and Stiffness subscales and Total score22, and the Clinical Global Impression of Severity (CGI-S) scale21.
Safety measures assessed during the double-blind treatment phase included treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), the Columbia-Suicide Severity Rating Scale (C-SSRS), assessment of falls using solicited questioning, standard laboratory assessments, vital signs, and discontinuation rates due to adverse events.

**Statistical analyses**

Sample size was determined based on 90% power to detect a difference of 0.73 points with a standard deviation of 2.2 between duloxetine and placebo in the reduction of pain severity as measured by the BPI 24-hour Average Pain rating. A total sample size of 400 patients (200 patients per group) was planned using a between-treatment group t-test, two-sided alpha of 0.05, and a likely discontinuation rate of 4%.

The intent-to-treat principle was used in the analyses of all efficacy variables (i.e., patients were analyzed by the treatment groups to which patients were randomly assigned, even if the patient did not take the assigned treatment, did not receive the correct treatment, or did not comply with the protocol).

For efficacy variables, analyses included all randomized patients with a baseline and at least 1 postbaseline observation. For the primary objective, change from baseline to endpoint on the BPI 24-hour Average Pain rating was analyzed using a mixed-model-repeated-measures (MMRM) approach. In general, when a repeated measures analysis was used, the model included the fixed categorical effects of treatment, pooled investigative site, visit, and treatment-by-visit interaction, as well as the fixed continuous covariates of the baseline value of the variable being analyzed and baseline value of the variable being analyzed-by-visit interaction. Analysis of covariance (ANCOVA) using a last-observation-carried-forward (LOCF) approach for imputation of missing data was applied as a supportive analysis. When an ANCOVA model was
used to analyze a continuous variable, the model contained the main effects of treatment and pooled investigative site, and appropriate baseline value as covariates. Change from baseline to endpoint for other efficacy variables was analyzed using a similar approach. A Fisher exact test was applied to categorical variables.

As described above, analysis of proportions of patients experiencing ≥30% and ≥50% reductions at endpoint (using LOCF) was performed for BPI 24-hour Average Pain. The proportions of patients reporting endpoint responses of either “much better” or “very much better” on the PGI-Improvement scale were also calculated.

All randomized patients who received at least one dose of a trial treatment were included in the safety analyses (Safety Set). Investigative sites with fewer than 4 patients with postbaseline data were pooled for statistical analysis purposes. All tests of treatment effects were conducted at a two-sided alpha level of 0.05. Confidence intervals (CIs) of between-group differences for dichotomous outcomes were calculated using the method of Agresti and Caffo. Analyses were conducted with SAS Version 9.2 (The SAS Institute, Inc., Cary, NC).

**Results**

*Patient disposition, baseline demographics, and disease characteristics*

Of 481 patients who entered the study, a total of 407 were randomized to duloxetine (N=205) or placebo (N=202) treatment groups, respectively (Figure 1). A total of 166 (81.0%) patients from the duloxetine group and 176 (87.1%) patients from the placebo group completed the 13-week double-blind treatment phase (group difference [95% CI]=−6.2% [-13.2%, 0.9%]; p=0.105).

Baseline demographic characteristics were comparable between treatment groups (Table 1).
The mean age of the patients was 60.5 years. Most of the patients were female (76.4%), and mean duration of pain due to OA since onset was 7.99 years. For most patients (404/407, 99.3%), the index joint was a knee. No significant differences in baseline disease characteristics were reported between the treatment groups (Table 1).

Efficacy and health outcomes measures

There was a statistically significant improvement in both the duloxetine (least-squares [LS] mean change [95% CI]= -2.23 [-2.45, -2.01]; p<0.001) and placebo (LS mean change [95% CI]= -1.73 [-1.95, -1.51]; p<0.001) treatment groups on the BPI 24-hour Average Pain rating at endpoint when compared with baseline scores. Additionally, duloxetine-treated patients experienced statistically significantly greater pain reduction compared with placebo-treated patients on the BPI 24-hour Average Pain rating at endpoint (difference between duloxetine and placebo=-0.5 and 95% CI [-0.80, -0.20]) (Table 2, Figure 2).

A significantly greater percentage of duloxetine-treated patients, compared to placebo-treated patients, experienced a ≥30% reduction in pain from baseline based on the BPI 24-hour Average Pain severity rating (63.4% vs. 49.7%; group difference [95% CI]=13.7% [4.0%, 23.4%]; p=0.008). A numerically higher percentage of duloxetine-treated patients (42.8%), compared with placebo-treated patients (34.5%), experienced a ≥50% reduction from baseline
in BPI 24-hour Average Pain severity, but this difference was not statistically significant (group difference [95% CI]=8.3% [-1.3%, 17.9%]).

The BPI-Severity measures of Worst Pain and Pain Right Now were also statistically significantly improved (decreased) in duloxetine-treated patients compared with placebo-treated patients, while Least Pain was not significantly different between the treatment groups (Table 2). The improvement in the BPI-Interference Average Rating was significantly greater in the duloxetine-treated patients, compared with the placebo-treated group. The individual items of General Activity, Mood, and Walking Ability of the BPI-Interference scale showed significantly greater decreases in duloxetine-treated patients compared with placebo-treated patients, but the Normal Work, Relations with Other People, Sleep, and Enjoyment of Life items did not (Table 2).

For PGI-Improvement, the LS mean for the duloxetine group was statistically significantly greater than for the placebo group (Table 2). In addition, categorical analysis of response rates based on PGI-Improvement showed a significantly greater percentage of duloxetine-treated patients reported feeling either “much better” or “very much better” at endpoint compared with placebo-treated patients (38.7% vs. 20.4%; group difference [95% CI]=18.3% [9.4%, 27.1%]; p<0.001) (Figure 3). The distribution of all response categories for both treatment groups is also presented in Figure 3.

Mean WOMAC Total scores, as well as all subscale scores (Pain, Physical Function, Stiffness), were significantly more improved for duloxetine- vs. placebo-treated patients. In addition, CGI-S scores were significantly more improved for duloxetine- vs. placebo-treated patients (Table 2).
Safety measures

A total of 204 (51.4%) patients experienced ≥1 TEAE during the double-blind treatment phase. The overall incidence of TEAEs was 60.8% in duloxetine-treated patients and 41.9% in placebo-treated patients (group difference [95% CI]=18.9% [9.3%, 28.5%]; p<0.001). In duloxetine-treated patients, the most frequently observed TEAEs were dry mouth, somnolence, nausea, constipation, dizziness, decreased appetite, insomnia, abnormal faeces, and thirst (Table 3).

No deaths or suicide-related events were reported. No SAEs were reported in duloxetine-treated patients; three SAEs were reported in placebo-treated patients (0.0% vs. 1.5%; group difference [95% CI]=-1.5% [-3.7%, 0.7%]). No significant difference was found between duloxetine- and placebo-treated patients in the incidence of adverse events that led to discontinuation (9.0% vs. 4.5%, respectively; group difference [95% CI]=4.5% [-0.6%, 9.6%]; p=0.109). A larger percentage of patients in the duloxetine group, compared with the placebo group, reported treatment-emergent falls, but this difference was not statistically significant (3.0% vs. 0.5%; group difference [95% CI]=2.5% [-0.4%, 5.4%]; p=0.122).

No clinically relevant differences between treatment groups were noted in routine laboratory parameters or vital signs. No treatment-emergent abnormal liver function tests were reported for any duloxetine-treated patients; 1 patient in the placebo-treated group showed alanine aminotransferase to be ≥10 times the upper limit of normal (0.0% vs. 0.5%; group difference [95% CI]=-0.5% [-2.3%, 1.3%]).

Concomitant short-acting analgesics
Overall, the percentage of patients using short-acting analgesics was low, but significantly greater in the placebo group compared with the duloxetine group (3.5% vs. 0.5%; group difference [95% CI]=-3.0% [-6.0%, 0.0%]; p=0.036). The following such medications were used by patients in this study: ibuprofen, celecoxib, diclofenac diethylamine, meloxicam, paracetamol, tetrahydropalmatine, and unspecified herbals.

**Discussion**

**Efficacy**

In this study of OA-related pain in China, duloxetine-treated patients demonstrated significantly greater reduction (compared with placebo-treated patients) in 24-hour Average Pain, as measured on the BPI. The magnitude of the decrease in pain ratings observed in this study is slightly lower than those in previous global OA studies. There are two possible explanations for this difference. First, the Average Pain rating at baseline was lower in the present study (5.4) compared with the previous studies (6.0–6.1), suggesting that, for the present study population, there was less room for improvement. Although no statistically significant interaction was observed between pain reduction and baseline pain severity in either the present study, patients with more severe pain at baseline did report a numerically greater pain reduction compared with those with less pain at baseline. Second, in the previous studies, the dose of duloxetine was escalated to 120 mg QD for some patients at week 7, which may have led to greater pain reduction. The magnitude of pain reduction found in the present study was also somewhat lower than that reported by Frakes et al., which compared the efficacy of duloxetine to placebo in patients already taking an NSAID for pain. However, that study also allowed dose escalation to 120 mg/day duloxetine.
A significantly greater percentage of duloxetine-treated patients (compared with placebo-treated patients) had a ≥30% reduction Average Pain Severity, as measured on the BPI. The 30% cut-off is consistent with moderately important improvement, according to recommendations from IMMPACT (the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials).  

A significantly greater percentage of duloxetine-treated patients rated their pain as “much better” or “very much better” at endpoint on the PGI-Improvement scale and mean improvement on this scale was significantly greater for duloxetine- versus placebo-treated patients. Most of the other secondary measures were statistically significant as well. The WOMAC (including the Total Score as well as the Pain Physical Function, and Stiffness subscales) and CGI-S showed greater improvement in the duloxetine-treated group compared with the placebo-treated group. On the BPI-Severity scale, and the Worst Pain and Right Now Pain subscales, but not the Least Pain subscale, showed more improvement in the duloxetine group. For health outcomes, on the BPI-Interference scale, the average score, as well as the General Activity, Mood, and Walking Ability subscales showed greater improvement in the duloxetine group. However, the Normal Work, Relations with Other People, Sleep, and Enjoyment of Life subscales were not significantly more improved in the duloxetine group, compared with the placebo group. This is not unexpected since this study was only powered to demonstrate difference in BPI 24-hour Average Pain changes between duloxetine and placebo groups.

**Safety**

The safety profile of duloxetine observed in this study is consistent with its previously published safety profile across indications and populations. The TEAEs were reported at rates similar to previous studies, and no new TEAEs were reported. In addition, there were no clinically relevant differences between treatment groups in laboratory parameters or vital signs. The relatively benign nature of the reported adverse events is an important advantage of duloxetine,
compared to the risks of many other pain medications for OA. For example, treatment with NSAIDs is associated with gastrointestinal, renal, hepatic, and cardiovascular adverse events. There are safety concerns with opioids use, including respiratory depression, constipation, and cognitive impairment.

No deaths or suicide-related events were reported. There were significantly more adverse events reported by duloxetine-treated patients, but the discontinuations due to adverse events were similar between groups.

**Limitations**

Compared with the typical treatment duration for pain associated with OA, the duration of this study period was relatively short (13-week treatment period). However, there are ethical and practical concerns regarding conducting a longer-term trial using placebo as a comparator. Long-term open-label studies may provide more information about the long-term safety and maintenance of efficacy of duloxetine in the treatment of OA.

**Conclusions**

The results from the present study demonstrate the efficacy and safety of duloxetine 60 mg QD in treating pain in Chinese patients with OA. Duloxetine can therefore be considered a useful resource in the treatment armamentarium of clinicians for these patients. Duloxetine 60 mg QD was shown to have a safety profile consistent with that found in other duloxetine trials. This study strengthens the data supporting efficacy and safety of duloxetine in painful conditions by the addition of a Chinese population suffering pain due to OA.

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Author contributions

All authors contributed to 1) the acquisition, analysis, or interpretation of data and 2) the drafting and/or critical revision of this manuscript. In addition, C-NW conducted the statistical analyses; VS, LY, and J-NW contributed to the conception or design of the study. All authors approved the final submitted version of the manuscript. Dr. Li Yue (yue_li_sh@lilly.com) takes primary responsibility for the integrity of the work as a whole.

Role of the funding source

This study was funded by Eli Lilly and Company (and/or one of its subsidiaries) which is responsible for the study design, and was responsible for the collection, analysis and interpretation of data, the manuscript development, and the decision to submit the manuscript for publication.

Conflict of interest

Drs. Guochun Wang, LiQi Bi, Xiangpei Li, Zhijun Li, Dongbao Zhao, Jinwei Chen, and Dongyi He had no conflicts of interest to report. Drs. Héctor Dueñas, Li Yue, Chia-Ning Wang, and Vladimir Skljarevski, are employees and minor shareholders of Eli Lilly and Company.
REFERENCES


Figure legends

Figure 1. Patient disposition.

Figure 2. Change in mean of 24-hour BPI average pain severity.

Abbreviations: BPI=brief pain inventory; CI=confidence interval; LS Mean=least-squares mean

Figure 3. Response to treatment* and proportions of patient responses to treatment on the PGI-
Improvement Scale.

*Note: Response to treatment was defined as endpoint PGI-Improvement rating of either ‘much
better’ or ‘very much better’.

*p-value assesses placebo versus duloxetine for response categories overall (a Fisher exact
test)

Abbreviations: N=Number of randomized patients with nonmissing data at baseline and
endpoint; PGI-Improvement=Patient’s Global Impressions of improvement.
### Table 1. Patient demographics and baseline assessments

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Duloxetine</th>
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<tbody>
<tr>
<td></td>
<td>N=202</td>
<td>N=205</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>59.8 (8.4)</td>
<td>61.2 (8.2)</td>
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<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>151 (74.8)</td>
<td>160 (78.0)</td>
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<tr>
<td>BMI, kg/m(^2), mean (SD)</td>
<td>25.4 (3.7)</td>
<td>25.4 (3.2)</td>
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<tr>
<td>Duration of OA Diagnosis, years, mean (SD)</td>
<td>2.7 (4.2)</td>
<td>2.9 (4.4)</td>
</tr>
<tr>
<td>Location of OA, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip</td>
<td>2 (1.0)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Knee</td>
<td>200 (99.0)</td>
<td>204 (99.5)</td>
</tr>
<tr>
<td>Duration of OA Pain (years), mean (SD)</td>
<td>7.8 (7.1)</td>
<td>8.2 (7.8)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI=body mass index; N=number of patients in group; n=number of affected patients; OA=osteoarthritis; SD=standard deviation.

Means were analyzed using a Type III sum of squares analysis of variance. Frequencies were analyzed using a Fisher exact test.
Table 2. Summary of secondary efficacy measures and health outcome measures

<table>
<thead>
<tr>
<th>Variables</th>
<th>Scale Range</th>
<th>Placebo Mean (SD)</th>
<th>Placebo LS Mean Change (95% CI)</th>
<th>Duloxetine Mean (SD)</th>
<th>Duloxetine LS Mean Change (95% CI)</th>
<th>Difference (95% CI)</th>
<th>p-Value</th>
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<tr>
<td>BPI-Severity</td>
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<td></td>
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<td>24-hour Average Pain</td>
<td>0-10</td>
<td>197 5.41 (1.21)</td>
<td>-1.73 (-1.95, -1.51)</td>
<td>194 5.49 (1.27)</td>
<td>-2.23 (-2.45, -2.01)</td>
<td>-0.50 (-0.80, -0.20)</td>
<td>0.001</td>
</tr>
<tr>
<td>Worst Pain</td>
<td>0-10</td>
<td>197 6.76 (1.39)</td>
<td>-2.00 (-2.27, -1.73)</td>
<td>194 6.9 (1.41)</td>
<td>-2.71 (-2.98, -2.44)</td>
<td>-0.71 (-1.07, -0.34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Least Pain</td>
<td>0-10</td>
<td>197 3.59 (1.84)</td>
<td>-1.20 (-1.44, -0.96)</td>
<td>194 3.58 (1.92)</td>
<td>-1.48 (-1.72, -1.24)</td>
<td>-0.29 (-0.60, 0.03)</td>
<td>0.073</td>
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<tr>
<td>Pain Right Now</td>
<td>0-10</td>
<td>197 4.83 (2.10)</td>
<td>-1.74 (-1.99, -1.49)</td>
<td>194 4.95 (2.14)</td>
<td>-2.21 (-2.48, -1.94)</td>
<td>-0.47 (-0.82, -0.11)</td>
<td>0.010</td>
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<tr>
<td>BPI-Interference</td>
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<tr>
<td>Average Rating</td>
<td>0-10</td>
<td>197 3.58 (1.89)</td>
<td>-1.36 (-1.56, -1.16)</td>
<td>194 3.42 (1.95)</td>
<td>-1.63 (-1.83, -1.43)</td>
<td>-0.27 (-0.53, -0.02)</td>
<td>0.036</td>
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<tr>
<td>General Activity</td>
<td>0-10</td>
<td>197 5.34 (2.18)</td>
<td>-1.83 (-2.10, -1.56)</td>
<td>194 5.23 (2.28)</td>
<td>-2.39 (-2.66, -2.12)</td>
<td>-0.56 (-0.94, -0.19)</td>
<td>0.003</td>
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<tr>
<td>Mood</td>
<td>0-10</td>
<td>197 2.82 (2.62)</td>
<td>-1.04 (-1.29, -0.79)</td>
<td>194 2.60 (2.61)</td>
<td>-1.43 (-1.68, -1.18)</td>
<td>-0.39 (-0.74, -0.05)</td>
<td>0.027</td>
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<tr>
<td>Walking Ability</td>
<td>0-10</td>
<td>197 5.25 (2.31)</td>
<td>-1.88 (-2.13, -1.63)</td>
<td>194 5.28 (2.23)</td>
<td>-2.35 (-2.62, -2.08)</td>
<td>-0.47 (-0.82, -0.11)</td>
<td>0.011</td>
</tr>
<tr>
<td>Variable</td>
<td>Code</td>
<td>n</td>
<td>Mean (SD)</td>
<td>CI Lower</td>
<td>CI Upper</td>
<td>p-Value</td>
<td>CI Lower</td>
</tr>
<tr>
<td>------------------------</td>
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<td>----------</td>
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</tr>
<tr>
<td>Normal Work 0-10</td>
<td>197</td>
<td>-1.76 (-2.03, -1.49)</td>
<td>-2.06 (-2.33, -1.79)</td>
<td>-0.31 (-0.68, 0.06)</td>
<td>0.105</td>
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<tr>
<td>Relations with Other People 0-10</td>
<td>197</td>
<td>-0.84 (-1.06, -0.62)</td>
<td>-0.90 (-1.12, -0.68)</td>
<td>-0.07 (-0.34, 0.21)</td>
<td>0.642</td>
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<tr>
<td>Sleep 0-10</td>
<td>177</td>
<td>-0.99 (-1.24, -0.74)</td>
<td>-1.21 (-1.48, -0.94)</td>
<td>-0.22 (-0.57, 0.14)</td>
<td>0.228</td>
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<tr>
<td>Enjoyment of Life 0-10</td>
<td>197</td>
<td>-1.07 (-1.32, -0.82)</td>
<td>-1.14 (-1.39, -0.89)</td>
<td>-0.06 (-0.40, 0.27)</td>
<td>0.713</td>
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<tr>
<td>PGI-Improvement 1-7</td>
<td>--</td>
<td>3.09 (2.95, 3.23)</td>
<td>2.73 (2.59, 2.87)</td>
<td>-0.36 (-0.54, -0.19)</td>
<td>&lt;0.001</td>
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<tr>
<td>WOMAC</td>
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<tr>
<td>Total 0-96</td>
<td>182</td>
<td>-10.09 (-11.85, -8.33)</td>
<td>-13.58 (-15.38, -11.78)</td>
<td>-3.49 (-5.62, -1.35)</td>
<td>0.001</td>
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<tr>
<td>Pain 0-20</td>
<td>182</td>
<td>-2.32 (-2.73, -1.91)</td>
<td>-3.03 (-3.44, -2.62)</td>
<td>-0.71 (-1.21, -0.21)</td>
<td>0.005</td>
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<tr>
<td>Physical Function 0-68</td>
<td>182</td>
<td>-7.28 (-8.59, -5.97)</td>
<td>-9.64 (-10.97, -8.31)</td>
<td>-2.36 (-3.95, -0.78)</td>
<td>0.004</td>
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<tr>
<td>Stiffness 0-8</td>
<td>182</td>
<td>-0.44 (-0.64, -0.24)</td>
<td>-0.83 (-1.03, -0.63)</td>
<td>-0.39 (-0.62, -0.16)</td>
<td>&lt;0.001</td>
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<td></td>
</tr>
<tr>
<td>CGI-S 1-7</td>
<td>196</td>
<td>-0.53 (-0.63, -0.43)</td>
<td>-0.81 (-0.91, -0.71)</td>
<td>-0.28 (-0.41, -0.15)</td>
<td>&lt;0.001</td>
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<td></td>
</tr>
</tbody>
</table>

a LS Mean

b LS Mean Difference

Abbreviations: BPI-Severity=Brief Pain Inventory of Severity; BPI-Interference=Brief Pain Inventory-Interference; CGI-S=Clinical Global Impression of Severity; CI=confidence interval; LS=least-squares; LOCF=last observation carried forward; MMRM=mixed-model repeated measures; n=number of randomized patients with nonmissing data for MMRM and number of patients with a
baseline and at least 1 nonmissing postbaseline value for LOCF; PGI-Improvement=Patient Global Impression of Improvement; SE=standard error; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.
Table 3. Treatment-emergent adverse events experienced by ≥5% of duloxetine-treated patients or that were statistically different between treatment groups

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Duloxetine</th>
<th>Group Difference</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=198</td>
<td>N=199</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td>Patients with ≥1 TEAE</td>
<td>83 (41.9)</td>
<td>121 (60.8)</td>
<td>18.9 (9.3, 28.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>11 (5.6)</td>
<td>31 (15.6)</td>
<td>10.0 (4.0, 16.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>Somnolence</td>
<td>10 (5.1)</td>
<td>28 (14.1)</td>
<td>9.0 (3.2, 14.8)</td>
<td>0.003</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9 (4.5)</td>
<td>20 (10.1)</td>
<td>5.5 (0.3, 10.7)</td>
<td>0.052</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (2.5)</td>
<td>24 (12.1)</td>
<td>9.5 (4.4, 14.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Constipation</td>
<td>5 (2.5)</td>
<td>21 (10.6)</td>
<td>8.0 (3.1, 13.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>2 (1.0)</td>
<td>16 (8.0)</td>
<td>7.0 (2.8, 11.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2 (1.0)</td>
<td>11 (5.5)</td>
<td>4.5 (0.8, 8.2)</td>
<td>0.020</td>
</tr>
<tr>
<td>Abnormal Faeces</td>
<td>1 (0.5)</td>
<td>8 (4.0)</td>
<td>3.5 (0.3, 6.7)</td>
<td>0.037</td>
</tr>
<tr>
<td>Thirst</td>
<td>0</td>
<td>7 (3.5)</td>
<td>3.5 (0.6, 6.4)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Abbreviations: CI=confidence interval; N=number of patients in group; n=number of affected patients; TEAE=treatment-emergent adverse event

Frequencies were analyzed by a Fisher exact test

The table displays the TEAEs (treatment phase) in ≥5% of duloxetine-treated patients or that were statistically different between duloxetine and placebo.
Figure 1  Patient disposition.
Figure 2 Change in mean of 24-hour BPI Average Pain Severity.

Abbreviations: BPI=brief pain inventory; CI=confidence interval; LS Mean=least-squares mean; N=number of patients.
Figure 3  Proportions of patient responses to treatment on the PGI-Improvement Scale.

*p-value assesses placebo versus duloxetine for response categories overall (a Fisher exact test)

Abbreviations: N=Number of randomized patients with nonmissing data at baseline and endpoint; PGI-Improvement=Patient’s Global Impressions of improvement.
Supplemental Table 1.

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