Osteoarthritis and Cartilage 25 (2017) 832–838

Osteoarthritis and Cartilage

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

G. Wang †, L. Bi ‡, X. Li §, Z. Li ||, D. Zhao ¶, J. Chen #, D. He ††, C.-N. Wang ‡‡, H. Dueñas §§, V. Skljarevski |||, L. Yue ¶¶ *

† *Rheumatology Department, China-Japan Friendship Hospital, Beijing, PR China*
‡ *Rheumatology Department, China-Japan Union Hospital of Jilin University, Changchun, PR China*
§ *Rheumatology Department, Anhui Provincial Hospital, Hefei, PR China*
|| *Rheumatology Department, Affiliated Hospital of Bengbu Medical College, Bengbu, PR China*
¶ *Rheumatology Department, Shanghai Changhai Hospital, The 2nd Military Medical University, Shanghai, PR China*
# *Rheumatology Department, The Second Xiangya Hospital of Central South University, Changsha, PR China*
†† *Rheumatology Department, Shanghai Guanghua Hospital, Shanghai, PR China*
‡‡ *Asian-Pacific Statistical Sciences, Lilly Suzhou Pharmaceutical Co. Ltd., Shanghai Branch, Shanghai, PR China*
§§ *EMBU Regional Medical Affairs, Eli Lilly de Mexico, Mexico City, Mexico*
||| *Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, USA*
¶¶ *Medical Department, Lilly Suzhou Pharmaceutical Co. Ltd., Shanghai Branch, Shanghai, PR China*

ARTICLE INFO

Article history:
Received 1 September 2016
Accepted 20 December 2016

Keywords:
Duloxetine
Osteoarthritis
Chronic pain
Treatment
Chinese

SUMMARY

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-h 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 was female; mean age was 60.5 years. Duloxetine-treated patients reported significant pain reduction, compared with placebo treatment, on the BPI 24-h Average Pain rating (least-squares mean (LS Mean) change from baseline to endpoint [95% confidence interval (CI)], 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).

* Address correspondence and reprint requests to: L. Yue, Lilly Suzhou Pharmaceutical Co. Ltd., Shanghai Branch 21F, 1 Corporate Avenue, 222 Hu Bin Road, Shanghai, 200021, PR China.
E-mail addresses: guochunwang@hotmail.com (G. Wang), biliqi66@126.com (L. Bi), lixiangpei55@126.com (X. Li), lizhijundr@126.com (Z. Li), dongbaozhao@163.com (D. Zhao), jinwei7310@163.com (J. Chen), dongyihe@medmail.com.cn (D. He), wang_jia_ning_sh@lilly.com (C.-N. Wang), duenas_hector@lilly.com (H. Dueñas), skljarevski_vladimir@lilly.com (V. Skljarevski), yue_li_sh@lilly.com (L. Yue).

http://dx.doi.org/10.1016/j.joca.2016.12.025

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 ≥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 ≥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 ≥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[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-h 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-h 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 h 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 1 of the following 3 conditions: age >50, morning stiffness <30 min, or crepitus[18]. For the hip, OA disease criteria included hip pain and at least 2 of the following 3 conditions: erythrocyte sedimentation rate <20 mm/h, femoral or acetabular osteophytes (with radiographic evidence), or radiographic joint space narrowing (superior, axial and/or medial)[19].

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 5 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 4. 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-h Average Pain rating. The BPI is a self-reported scale that measures the severity of pain and the interference of pain on function[20]. In addition to Average Pain, the Brief Pain Inventory of Severity (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 Brief Pain Inventory-Interference (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-h Average Pain severity ratings. Other measures included the Patient Global Impression of Improvement (PGI-Improvement)[21], the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Physical Function, Pain, and Stiffness subscales and Total score[22], and the Clinical Global Impression of Severity (CGI-S) scale[21].

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 (SD) of 2.2 between duloxetine and placebo in the reduction of pain severity as measured by the BPI 24-h Average Pain rating. A total sample size of 400 patients (200 patients per group) was planned using a between-treatment group *t*-test, 2-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-h 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-h 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 1 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 2-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[23]. 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 (Fig. 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 I). 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 I).

Efficacy and health outcomes measures

There was a statistically significant improvement in both the duloxetine (least-squares mean [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-h 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-h Average Pain rating at endpoint (difference between duloxetine and placebo = −0.5% and 95% CI [−0.80, −0.20]) (Table II, Fig. 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-h Average Pain

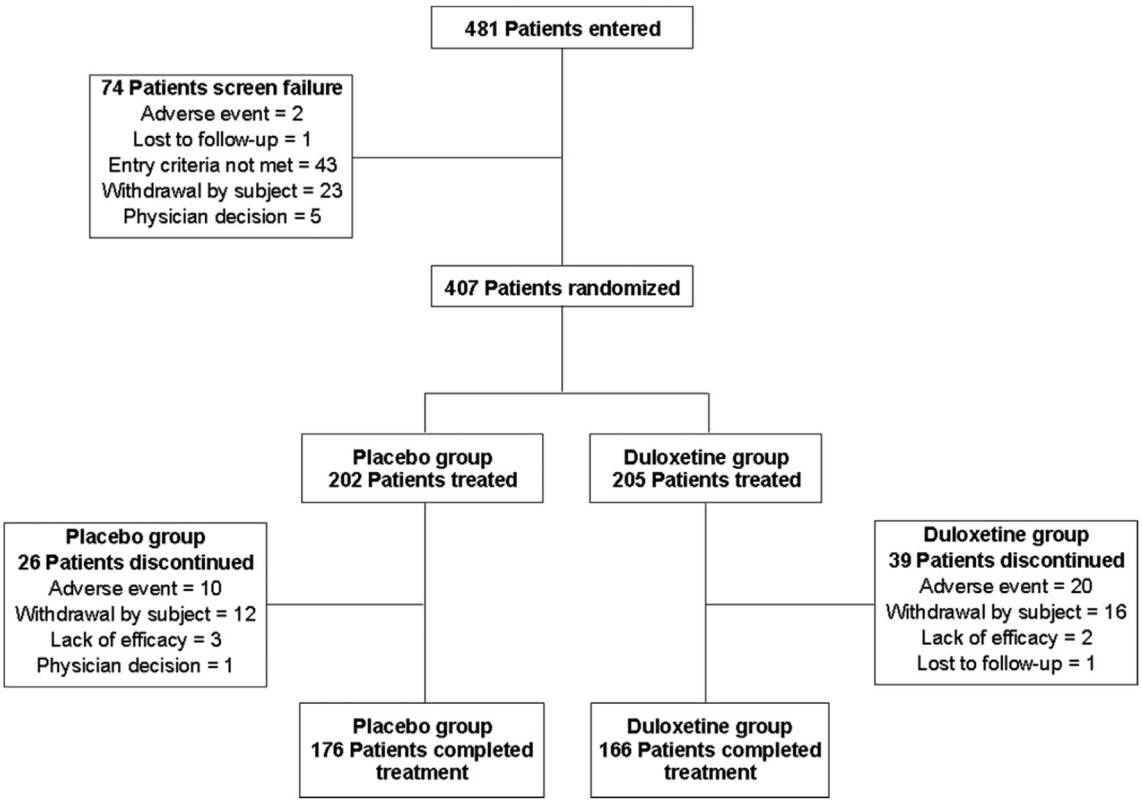

Fig. 1. Patient disposition.

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-h 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 II). 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 II).

For PGI-Improvement, the LS mean for the duloxetine group was statistically significantly greater than for the placebo group (Table II). 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%]; $P < 0.001$) (Fig. 3). The distribution of all response categories for both treatment groups is also presented in Fig. 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 II).

Table I
Patient demographics and baseline assessments

	Placebo $N = 202$	Duloxetine $N = 205$
Age, years, mean (SD)	59.8 (8.4)	61.2 (8.2)
Gender, *n* (%)		
Female	151 (74.8)	160 (78.0)
BMI, kg/m^2, mean (SD)	25.4 (3.7)	25.4 (3.2)
Duration of OA diagnosis, years, mean (SD)	2.7 (4.2)	2.9 (4.4)
Location of OA, *n* (%)		
Hip	2 (1.0)	1 (0.5)
Knee	200 (99.0)	204 (99.5)
Duration of OA pain (years), mean (SD)	7.8 (7.1)	8.2 (7.8)

Abbreviations: BMI = body mass index; N = number of patients in group; n = number of affected patients.
Means were analyzed using a Type III sum of squares analysis of variance. Frequencies were analyzed using a Fisher exact test.

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 III).

Table II
Summary of secondary efficacy measures and health outcome measures

Variables	Scale range	Placebo				Duloxetine				LS mean change difference (95% CI)	*P*-value
		Baseline		N	Change from baseline	Baseline		N	Change from baseline		
		N	Mean (SD)		LS mean change (95% CI)	N	Mean (SD)		LS mean change (95% CI)		
BPI-Severity											
24-h Average Pain	0–10	197	5.41 (1.21)	177	−1.73 (−1.95, −1.51)	194	5.49 (1.27)	172	−2.23 (−2.45, −2.01)	−0.50 (−0.80, −0.20)	0.001
Worst Pain	0–10	197	6.76 (1.39)	177	−2.00 (−2.27, −1.73)	194	6.9 (1.41)	172	−2.71 (−2.98, −2.44)	−0.71 (−1.07, −0.34)	<0.001
Least Pain	0–10	197	3.59 (1.84)	177	−1.20 (−1.44, −0.96)	194	3.58 (1.92)	172	−1.48 (−1.72, −1.24)	−0.29 (−0.60, 0.03)	0.073
Pain Right Now	0–10	197	4.83 (2.10)	177	−1.74 (−1.99, −1.49)	194	4.95 (2.14)	172	−2.21 (−2.48, −1.94)	−0.47 (−0.82, −0.11)	0.010
BPI-Interference											
Average Rating	0–10	197	3.58 (1.89)	177	−1.36 (−1.56, −1.16)	194	3.42 (1.95)	172	−1.63 (−1.83, −1.43)	−0.27 (−0.53, −0.02)	0.036
General Activity	0–10	197	5.34 (2.18)	177	−1.83 (−2.10, −1.56)	194	5.23 (2.28)	172	−2.39 (−2.66, −2.12)	−0.56 (−0.94, −0.19)	0.003
Mood	0–10	197	2.82 (2.62)	177	−1.04 (−1.29, −0.79)	194	2.60 (2.61)	172	−1.43 (−1.68, −1.18)	−0.39 (−0.74, −0.05)	0.027
Walking Ability	0–10	197	5.25 (2.31)	177	−1.88 (−2.13, −1.63)	194	5.28 (2.23)	172	−2.35 (−2.62, −2.08)	−0.47 (−0.82, −0.11)	0.011
Normal Work	0–10	197	4.94 (2.33)	177	−1.76 (−2.03, −1.49)	194	4.52 (2.52)	172	−2.06 (−2.33, −1.79)	−0.31 (−0.68, 0.06)	0.105
Relations with Other People	0–10	197	1.77 (2.30)	177	−0.84 (−1.06, −0.62)	194	1.62 (2.45)	172	−0.90 (−1.12, −0.68)	−0.07 (−0.34, 0.21)	0.642
Sleep	0–10	197	2.54 (2.64)	177	−0.99 (−1.24, −0.74)	194	2.39 (2.66)	172	−1.21 (−1.48, −0.94)	−0.22 (−0.57, 0.14)	0.228
Enjoyment of Life	0–10	197	2.38 (2.61)	177	−1.07 (−1.32, −0.82)	194	2.27 (2.71)	172	−1.14 (−1.39, −0.89)	−0.06 (−0.40, 0.27)	0.713
PGI-Improvement	1–7	–	–	177	3.09 (2.95, 3.23)*	–	–	172	2.73 (2.59, 2.87)*	−0.36 (−0.54, −0.19)†	<0.001
WOMAC											
Total	0–96	182	36.68 (13.95)	182	−10.09 (−11.85, −8.33)	184	37.35 (13.97)	184	−13.58 (−15.38, −11.78)	−3.49 (−5.62, −1.35)	0.001
Pain	0–20	182	7.67 (2.99)	182	−2.32 (−2.73, −1.91)	184	7.83 (2.96)	184	−3.03 (−3.44, −2.62)	−0.71 (−1.21, −0.21)	0.005
Physical Function	0–68	182	26.73 (10.36)	182	−7.28 (−8.59, −5.97)	184	27.17 (10.27)	184	−9.64 (−10.97, −8.31)	−2.36 (−3.95, −0.78)	0.004
Stiffness	0–8	182	2.28 (1.6)	182	−0.44 (−0.64, −0.24)	184	2.35 (1.72)	184	−0.83 (−1.03, −0.63)	−0.39 (−0.62, −0.16)	<0.001
CGI-S	1–7	196	4.15 (0.74)	177	−0.53 (−0.63, −0.43)	194	4.23 (0.75)	172	−0.81 (−0.91, −0.71)	−0.28 (−0.41, −0.15)	<0.001

Abbreviations: *N* = number of patients in group; SE = standard error; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
* LS mean.
† LS mean difference.

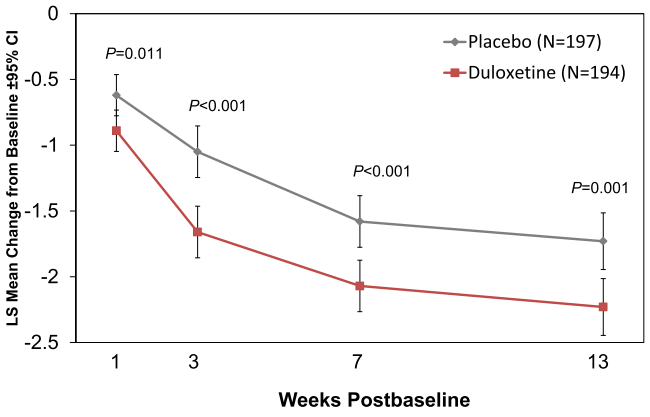

Fig. 2. Change in mean of 24-h BPI Average Pain severity. Abbreviations: *N* = number of randomized patients with nonmissing data at week 1 postbaseline.

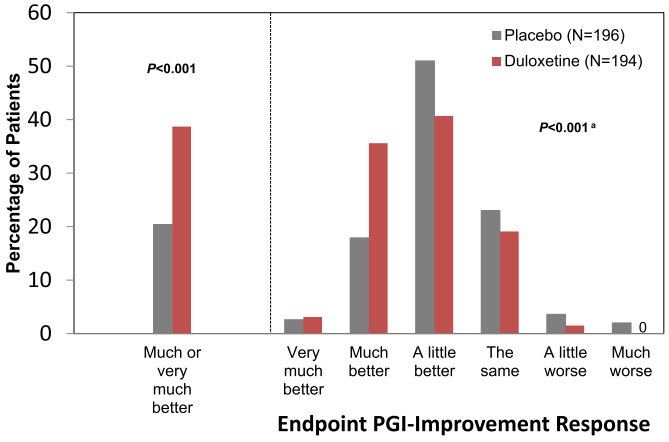

Fig. 3. Response to treatment* and proportions of patient responses to treatment on the PGI-Improvement Scale. *Note: Response to treatment was defined as endpoint PGI-Improvement rating of either 'much better' or 'very much better'. [a]*P*-value assesses placebo vs duloxetine for response categories overall (a *Fisher exact test*). Abbreviation: *N* = Number of randomized patients with nonmissing data at baseline and endpoint.

No deaths or suicide-related events were reported. No SAEs were reported in duloxetine-treated patients; 3 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, paramol-118, tetrahydropalmatine, and unspecified herbals.

Table III
TEAEs experienced by ≥ 5% of duloxetine-treated patients or that were statistically different between treatment groups

	Placebo $N = 198$ n (%)	Duloxetine $N = 199$ n (%)	Group difference (95% CI)	P-value
Patients with ≥1 TEAE	83 (41.9)	121 (60.8)	18.9 (9.3, 28.5)	<0.001
Dry mouth	11 (5.6)	31 (15.6)	10.0 (4.0, 16.1)	0.002
Somnolence	10 (5.1)	28 (14.1)	9.0 (3.2, 14.8)	0.003
Dizziness	9 (4.5)	20 (10.1)	5.5 (0.3, 10.7)	0.052
Nausea	5 (2.5)	24 (12.1)	9.5 (4.4, 14.7)	<0.001
Constipation	5 (2.5)	21 (10.6)	8.0 (3.1, 13.0)	0.002
Decreased appetite	2 (1.0)	16 (8.0)	7.0 (2.8, 11.2)	0.001
Insomnia	2 (1.0)	11 (5.5)	4.5 (0.8, 8.2)	0.020
Abnormal faeces	1 (0.5)	8 (4.0)	3.5 (0.3, 6.7)	0.037
Thirst	0	7 (3.5)	3.5 (0.6, 6.4)	0.015

Abbreviations: N = Number of randomized patients who received at least 1 dose of a trial treatment; n = number of affected patients. 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.

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-h 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[24,25]. There are 2 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.*[26], 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)[27].

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- vs 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-h 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[28]. The TEAEs were reported at rates similar to previous studies[28], 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[29]. 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[29].

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.

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 C-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.

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.

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.

Acknowledgments

This study was funded by Eli Lilly and Company and/or one of its subsidiaries. Manuscript development (Rodney Moore, PhD) and editing (Ms. Angela Lorio) services were provided by inVentiv Health Clinical, LLC, funded by Eli Lilly and Company.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.joca.2016.12.025.

References

1. Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice. Lancet 2011;377:2115–26, http://dx.doi.org/10.1016/S0140-6736(11)60243-2.
2. Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. Bull World Health Organ 2003;81:646–56.
3. Yu W, Xu L, Qin M, Zhang Y-q, Nevitt MC, Aliabadi P, *et al.* Epidemiology of the prevalence of elderly knee osteoarthritis in Beijing: comparison with that of whites in the United States. Chin J Radiol 2005;39:67–71.
4. Su Y, Zhu Z, Cai Y, Jin D, Xue Q. Epidemiological investigation of symptomatic osteoarthritis in middle-aged and senior residents in district of Guangzhou. Chin J Joint Surg (Electronic Version) 2010;4:438–44.
5. Chinese Medical Association. Rheumatology Branch [Title in Chinese] 2010.
6. Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P, *et al.* Standing committee for international clinical studies including therapeutic trials ESCISIT. EULAR recommendations 2003: an evidence based approach to the management of knee osteoarthritis: report of a task force of the standing committee for international clinical studies including therapeutic trials (ESCISIT). Ann Rheum Dis 2003;62:1145–55.
7. Bradley LA, Kersh BC, DeBerry JJ, Deutsch G, Alarcón GA, McLain DA. Lessons from fibromyalgia: abnormal pain sensitivity in knee osteoarthritis. Novartis Found Symp 2004;260:258–70. discussion 270–9.
8. Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. Neuron 2007;55:377–91.
9. Apkarian AV, Baliki MN, Geha PY. Towards a theory of chronic pain. Prog Neurobiol 2008;87:81–97, http://dx.doi.org/10.1016/j.pneurobio.2008.09.018.
10. Ren K, Dubner R. Neuron-glia crosstalk gets serious: role in pain hypersensitivity. Curr Opin Anaesthesiol 2008;21:570–9, http://dx.doi.org/10.1097/ACO.0b013e32830edbdf.
11. Sofat N, Ejindu V, Kiely P. What makes osteoarthritis painful? The evidence for local and central pain processing. Rheumatol (Oxford) 2011;50:2157–65, http://dx.doi.org/10.1093/rheumatology/ker283.
12. Basbaum AI, Fields HL. Endogenous pain control systems: brainstem spinal pathways and endorphin circuitry. Annu Rev Neurosci 1984;7:309–38.
13. Fields HL, Heinricher MM, Mason P. Neurotransmitters in nociceptive modulatory circuits. Annu Rev Neurosci 1991;14:219–45.
14. Bymaster FP, Lee TC, Knadler MP, Detke MJ, Iyengar S. The dual transporter inhibitor duloxetine: a review of its preclinical pharmacology, pharmacokinetic profile, and clinical results in depression. Curr Pharm Des 2005;11:1475–93.
15. Chan C, Yeo KP, Pan AX, Lim M, Knadler MP, Small DS. Duloxetine pharmacokinetics are similar in Japanese and Caucasian subjects. Br J Clin Pharmacol 2007;63:310–4.
16. Zhao RK, Cheng G, Tang J, Song J, Peng WX. Pharmacokinetics of duloxetine hydrochloride enteric-coated tablets in healthy Chinese volunteers: a randomized, open-label, single- and multiple-dose study. Clin Ther 2009;31(5):1022–36, http://dx.doi.org/10.1016/j.clinthera.2009.05.005.
17. Gao Y, Guo X, Han P, Li Q, Yang G, Qu S, *et al.* Treatment of patients with diabetic peripheral neuropathic pain in China: a double-blind randomised trial of duloxetine vs. placebo. Int J Clin Pract 2015;69(9):957–66, http://dx.doi.org/10.1111/ijcp.12641.
18. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, *et al.* The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the knee. Arthritis Rheum 1986;29:1039–49.
19. Altman R, Alarcón G, Appelrouth D, Bloch D, Borenstein D, Brandt K, *et al.* The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. Arthritis Rheum 1991;34:505–14.
20. Cleeland CS, Ryan KM. Pain assessment: global use of the brief pain inventory. Ann Acad Med Singapore 1994;23:129–38.
21. Guy W. ECDEU Assessment Manual for Psychopharmacology, Revised. Rockville, MD: National Institute of Mental Health, Psychopharmacology Research Branch; 1976.
22. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15:1833–40.
23. Agresti A, Caffo B. Simple and effective confidence intervals for proportions and differences of proportions result from adding two successes and two failures. Am Stat 2000;54:280–8.
24. Chappell AS, Desaiah D, Liu-Seifert H, Zhang S, Skljarevski V, Belenkov Y, *et al.* A double-blind, randomized, placebo-controlled study of the efficacy and safety of duloxetine for the treatment of chronic pain due to osteoarthritis of the knee. Pain Pract 2011;11:33–41, http://dx.doi.org/10.1111/j.1533-2500.2010.00401.x.
25. Chappell AS, Ossanna MJ, Liu-Seifert H, Iyengar S, Skljarevski V, Li LC, *et al.* Duloxetine, a centrally acting analgesic, in the treatment of patients with osteoarthritis knee pain: a 13-week, randomized, placebo-controlled trial. Pain 2009;146:253–60, http://dx.doi.org/10.1016/j.pain.2009.06.024.
26. Frakes EP, Risser RC, Ball TD, Hochberg MC, Wohlreich MM. Duloxetine added to oral nonsteroidal anti-inflammatory drugs for treatment of knee pain due to osteoarthritis: results of a randomized, double-blind, placebo-controlled trial. Curr Med Res Opin 2011;27:2361–72, http://dx.doi.org/10.1185/03007995.2011.633502.
27. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, *et al.* Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain 2008;9:105–21.
28. Eli Lilly and CompanyCymbalta® [US Package Insert]. Indianapolis, IN, 2004.
29. Fitzcharles MA, Lussier D, Shir Y. Management of chronic arthritis pain in the elderly. Drugs Aging 2010;27:471–90, http://dx.doi.org/10.2165/11536530-000000000-00000.