Safety and efficacy of duloxetine in Japanese patients with chronic knee pain due to osteoarthritis: an open-label, long-term, Phase III extension study

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Purpose: To assess long-term safety, tolerability, and efficacy of duloxetine in Japanese patients with chronic knee pain due to osteoarthritis.

Methods: In this open-label extension study (NCT02335346), Japanese patients with knee osteoarthritis and pain (Brief Pain Inventory [BPI] – Severity average pain score ≥2 at start of randomized trial) who had previously received duloxetine 60 mg/day or placebo for 14 weeks in a double-blind randomized trial entered the extension and received duloxetine 60 mg/day for 48 weeks. The primary outcome was safety/tolerability, secondary outcomes were change in BPI-S Severity (BPI-S) average pain, BPI-Interference (BPI-I), Patient Global Impression-Improvement (PGI-I), Clinical Global Impression-Improvement (CGI-I), 36-item Short-Form Health Survey (SF36), and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and exploratory outcomes were knee range of motion (efficacy outcome) and Kellgren–Lawrence grade (safety outcome).

Results: Of 323 patients who completed the randomized trial, 93 (50 placebo, 43 duloxetine) entered the extension. Most patients (85, 91.4%) experienced an adverse event, most commonly constipation, nasopharyngitis, somnolence, and dry mouth (≥10% of patients). There were eight serious adverse events in seven patients and no deaths. No obvious duloxetine-related changes were observed in laboratory tests, vital signs, or electrocardiograms. The change from baseline in BPI-S average pain score was significant throughout the extension. Significant reductions in BPI-I, PGI-I, CGI-I, WOMAC, and SF36 scores were also maintained through 52 weeks. There were no substantial changes in range of motion or Kellgren–Lawrence grade.

Conclusion: In Japanese patients with chronic knee pain due to osteoarthritis, long-term treatment with duloxetine was well tolerated and associated with sustained improvements in pain and health-related quality of life without radiographic deterioration.

Keywords: analgesics, chronic pain due to knee osteoarthritis, duloxetine, quality of life, Western Ontario and McMaster Universities Osteoarthritis Index

Introduction

Osteoarthritis (OA) is an increasingly common degenerative joint disease, with the worldwide age-standardized prevalence of OA increasing by 32.9% between 2005 and 2015. The prevalence of symptomatic (ie, with pain or stiffness) OA of the knee increases with age and obesity and is more common in women than in men. In nonobese adults in the USA, the prevalence of symptomatic knee OA ranges from 0.74% (men aged 25–34 years) to 14.97% (women aged ≥85 years). The lifetime risk of developing...
symptomatic knee OA in the USA has been estimated to range from 13.83% to 44.7%.

OA has substantial negative effects on morbidity and socioeconomic perspectives and is often associated with pain, functional impairment, and loss of quality of life (QoL), as well as reduced work productivity and high medical costs to patients.

The Research on Osteoarthritis/osteoporosis Against Disability (ROAD) study has investigated the characteristics of Japanese patients with knee OA. In this prospective cohort study, the overall prevalence of radiographic knee OA in Japanese people aged 40 years and older was 17.9% (21.5% in women and 11.6% in men). The results led the authors to estimate that >25 million Japanese people aged 40 years and older may have radiographic knee OA.

Knee pain was a common symptom in the ROAD study, observed in approximately half the patients with radiographic knee OA, with a prevalence of 5.0% in men and 11.3% in women aged 40 years and older. Among people aged 60 years and older, the risk of knee pain increases with the severity of OA (according to Kellgren–Lawrence [KL] grade).

Pharmacotherapy is one type of intervention that can reduce pain and improve QoL in patients with knee pain due to OA. In Japan, the currently available pharmacotherapy options include systemic and topical nonsteroidal anti-inflammatory drugs, acetaminophen, intraarticular hyaluronic acid, intraarticular steroids, and weak opioids. As knee OA is a chronic disease and its prevalence associated with aging, physicians need to assess the risk–benefit balance of pain medication prescribed to patients, primarily from the perspective of safety.

Duloxetine is a serotonin and noradrenaline-reuptake inhibitor that is approved in the USA as analgesia for chronic musculoskeletal pain, fibromyalgia, and diabetic neuropathic pain, and in Japan for chronic low back pain, fibromyalgia, diabetic neuropathic pain, and chronic pain due to OA. The recent Japanese approval of duloxetine for OA pain was supported in part by the results of a Phase III, double-blind, randomized, placebo-controlled trial conducted in Japanese patients with chronic OA associated with knee pain.

In this trial, 14 weeks of treatment with duloxetine (60 mg/day) significantly reduced pain intensity and improved health-related QoL (HRQoL). However, as knee OA and its associated pain are chronic conditions, it is important to evaluate the long-term efficacy and safety of duloxetine in the treatment of knee OA, which has not been previously reported. Here, we report the results of an open-label, 52-week extension of the randomized trial, which assessed the long-term safety and efficacy of duloxetine 60 mg/day in Japanese patients with knee pain due to OA.

Methods

This study was conducted at 28 medical institutions throughout Japan between January 2015 and March 2016. The study was approved by the institutional review board of each study site (Table S1) and conducted in compliance with the International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent.

Study design and treatment protocol

This was a multicenter, long-term, open-label, extension study (ClinicalTrials.gov: NCT02335346) of a previously conducted randomized, double-blind, placebo-controlled, Phase III trial of duloxetine in Japanese patients with chronic knee pain due to OA (NCT02248480). As described previously, patients in the double-blind trial were randomized (using an interactive Internet-response system and stochastic minimization) 1:1 to placebo or duloxetine (Cymbalta; Eli Lilly, Indianapolis, IN, USA) taken orally once daily after breakfast (Figure 1A). The dose of duloxetine was increased from 20 mg/day (1 week) to 40 mg/day (1 week) to the target dose of 60 mg/day (12 weeks). At the end of the 14-week treatment phase, patients entered a 1-week dose-tapering phase. After completing the 1-week dose-tapering phase, patients were invited to participate in this extension study (Figure 1A). There was no washout period before entering the extension. Duloxetine was increased to 60 mg/day over 2 weeks. Patients then received duloxetine 60 mg/day for 48 weeks. After completion of treatment in the extension study (or discontinuation), patients underwent tapering for 2 weeks, followed by an observational phase of 1 week. The use of analgesic medication was not restricted during the extension study. Other allowed and prohibited treatments/interventions were similar to those in the previous study.

Study population

The inclusion and exclusion criteria for the double-blind trial have been described previously. The main inclusion criteria were male and female outpatients aged 40–79 years with current OA based on American College of Rheumatology classification of idiopathic OA of the knee, pain for ≥14 days of each month for the previous 3 months, and Brief Pain Inventory-Severity (BPI-S) 24-hour average pain score ≥4.
A validated Japanese version of the BPI was used.13 Patients were excluded from this study if they had serious medical or neuropsychiatric disorders, clinically significant laboratory abnormalities, or electrocardiographic abnormalities; alanine aminotransferase/aspartate aminotransferase concentration ≥100 IU/L or total bilirubin ≥1.6 mg/dL; serum creatinine concentration ≥2 mg/dL, renal transplantation, or renal dialysis; diagnosis of rheumatoid arthritis, autoimmune disorder, uncorrected thyroid disease, uncontrolled narrow-angle glaucoma, history of uncontrolled seizures, or uncontrolled or poorly controlled hypertension; depression diagnosed by the Mini-International Neuropsychiatric Interview;14 invasive procedures (eg, proximal tibial osteotomy, total knee arthroplasty); suicidal ideation or attempt; or a primary painful condition that could interfere with assessment of the knee. Excluded medications were monoamine oxidase
inhibitor treatment within 14 days and analgesic agents (other
than nonsteroidal anti-inflammatory drugs or acetaminophen)
or other medication used for treatment of chronic pain.

Outcome measures
The primary outcome of the extension study was the safety
and tolerability of duloxetine, assessed by the incidence of
adverse events (AEs), serious AEs (SAEs), severity of AEs, and
rate of discontinuation due to an AE. AEs included those that
continued from the double-blind phase and those that occurred
after the start of the extension study. The Medical Dictionary
for Regulatory Activities version 17.1 was used to code and
summarize all AEs. Standard laboratory measures, vital signs,
body weight, and electrocardiography were also assessed.

The efficacy of duloxetine for pain reduction was assessed
by the BPI-S 24-hour average pain score, which uses a scale
ranging from 0 (no pain) to 10 (worst pain imaginable).13
Global improvement from baseline (start of the double-blind
phase) was assessed by using the Patient Global Impression
Improvement (PGI-I)15 and Clinical Global Impression-
Improvement (CGI-I) scales,16 recorded by patients and
physicians, respectively, and rated from 1 (very much better)
to 7 (very much worse).

HRQoL was assessed by patient-reported BPI-Interference
(BPI-I) with seven daily activities (general activities, walking
ability, normal work, mood, enjoyment of life, relationships
with people, and sleep), rated from 0 (does not interfere) to
10 (completely interferes);13 the Short-Form Health Survey
(SF36), consisting of 36 questions related to the patient’s
health status within eight subscales (physical functioning,
physical role limitations, emotional role limitations, general
health perceptions, social functioning, bodily pain, vitality,
and mental health) and rated from 0 to 100;17 and the Western
Ontario and McMaster Universities Osteoarthritis Index
(WOMAC), consisting of 24 questions pertaining to the patient’s
knee condition on three subscales (pain, stiffness,
and physical function), each on a 5-point (0–4) scale, with
lower scores indicating better knee condition.18 The Beck
Depression Inventory (BDI)-II, consisting of 21 items related
to symptoms of depression on a 4-point (0–3) scale,19 was also
assessed. Range of motion (ROM) of the knee, an exploratory
efficacy measure, was measured by goniometry. The KL grade,
an exploratory safety measure, was evaluated in one knee by
examination of radiography in the upright position.

Statistical analysis
A target sample size of 90 patients was set for this extension
study to allow for 60 patients treated with duloxetine for 1
year, assuming an estimated maximum withdrawal rate of
30%. The safety analysis population included all enrolled
patients who received at least one dose of study treatment.
The efficacy analysis population included all enrolled patients
who received at least one dose of study treatment and had
at least one BPI-S average pain-score measurement after
the start of treatment. Missing data were not imputed, and
a last observation carried forward approach was used for
end-point values. Baseline was defined as the start of
the double-blind phase. All safety and efficacy measurements
are summarized descriptively. Baseline characteristics and
ROM data are presented as number (%), mean (SD), and/or
median (range), safety data presented as number (%), and
efficacy data presented as mean value or mean change from
baseline, with 95% CI or SD.

Results
Patient disposition and baseline
characteristics
Of 323 patients who completed the 14-week, double-blind
study, a total of 93 patients (50 placebo, 43 duloxetine 60 mg)
entered the extension study (Figure 1B). Of these, 81 (87.1%)
completed the 52-week extension. The main reason for dis-
continuation from the extension study was an AE. The rate
of discontinuation due to an AE was greater in patients from
the placebo group of the double-blind phase (7 of 50, 14.0%)
than in patients from the duloxetine group (4 of 43, 9.3%). The
baseline characteristics of patients who entered the extension
study were similar to those of the overall study population in
the double-blind phase of the study (Table S2). Most (72%)
patients were female, with a mean age of 66.2 years, mean OA
duration of 4.8 years, and mean BPI-S average pain score of 4.9.

Safety and tolerability
Almost all (91.4%) patients reported an AE during the
extension study (Table 1). The most common AEs (reported
by ≥10% of patients) were constipation, nasopharyngitis,
somnolence, and dry mouth, consistent with the incidence
of these AEs during the double-blind phase among patients
receiving duloxetine.11 The incidence of AEs, especially con-
stipation, somnolence, and dry mouth, was greater in patients
who received placebo during the double-blind phase than in
those who received duloxetine. Most patients experienced a
mild (69 of 93, 74.2%) or moderate (12 of 93, 12.9%) AE,
and four (4.3%) patients had a severe AE (all were SAEs).

There was a total of eight SAEs in seven patients (7.5% of
patients) during the extension study: six of these patients
had received placebo during the double-blind phase. One
patient developed infectious enteritis (not considered related to the study drug) and loss of consciousness after a fall the next day (considered possibly related to the study drug). The other SAEs were intervertebral disk protrusion (two patients), progressive supranuclear palsy, lumbar spinal stenosis, femur fracture, and intestinal obstruction (one patient each). All SAEs were considered resolved or recovered by the end of the study, except for the progressive supranuclear palsy. No obvious changes attributable to duloxetine were observed in laboratory tests, vital signs, or electrocardiography findings.

### Efficacy and health-related QoL outcomes

As reported previously, during the double-blind phase the mean BPI-S average pain score decreased to a greater extent in duloxetine-treated patients than in placebo-treated patients (Figure 2). Importantly, mean BPI-S average pain score decreased further during the extension study, including in patients who had previously received duloxetine, and was maintained throughout the 52-week extension study. The change from baseline (before starting continuous, long-term administration of the study drug, ie, at the start of the double-blind phase) in BPI-S average pain score was significant (upper 95% CI was negative) at all time points during the extension study. Duloxetine treatment was associated with significant improvements from baseline in pain, stiffness, and physical function, as assessed by WOMAC scores (Figures 3A and S1), and these improvements were maintained during the extension study (Figure S1). Both PGI-I and CGI-I scores also improved during the extension study (Figure S2).

Comprehensive measures of HRQoL (BPI-I, SF36) significantly improved from the start of the double-blind phase to the end of the extension study (Figure 3). There were significant improvements in all BPI-I and SF36 profiles. The largest improvements occurred for items related to physical aspects of HRQoL, such as BPI-I general activities, walking ability, and normal work, and SF36 bodily pain, physical functioning, and physical role limitations. Further, items related to mental, emotional, and social aspects also improved significantly. There was also a small but significant improvement in BDI-II scores from the start of the double-blind phase to the end of the extension study.

### Exploratory analysis

Long-term treatment with duloxetine was not associated with any major changes in the ROM efficacy measure (Table 2) or the KL-grade safety measure (Table 3). A change in KL grade from baseline to the end of the extension study was observed in only seven patients, all of whom had received placebo during the double-blind phase (Table 3). KL grade worsened from KL1 or KL2 to KL3 in three patients and improved from KL3 to KL2 in four patients.

### Discussion

This is the first long-term study of duloxetine in the treatment of chronic knee pain due to OA. In this extension study of a
randomized placebo-controlled trial conducted in Japanese patients with knee OA, duloxetine was generally well tolerated, and there were no additional safety concerns with use for up to 65 weeks. Duloxetine treatment was associated with significant and sustained improvements in pain, stiffness, and physical function in terms of BPI-S average pain and WOMAC profiles. Importantly, there were also improvements in physical, mental, emotional, and social aspects of HRQoL (BPI-I and SF36 scores). These improvements in pain and HRQoL occurred without changes in the severity of OA, as assessed by KL grade. Studies of whether duloxetine is an effective alternative to other analgesics in the long-term treatment of knee pain due to OA are warranted. Long-term administration of analgesics is sometimes necessary in patients with knee OA, especially while they await surgical procedures.

The most common AEs observed in this extension study (constipation, nasopharyngitis, somnolence, and dry mouth) were also observed in the duloxetine group of the prior double-blind study. In the double-blind study, constipation, somnolence, and dry mouth, as well as nausea, decreased appetite, and malaise, occurred in >5% of duloxetine-treated patients, and at significantly higher incidence than in placebo-treated patients, and are thus considered duloxetine-related AEs. These duloxetine-related AEs were also observed in another 13-week, double-blind, randomized, placebo-controlled trial in Chinese patients with knee or hip pain due to OA who

**Figure 3** (A) Change from baseline to end point (week 65) in BPI-I, WOMAC, and BDI-II scores; (B) change from baseline to end point (week 65) in SF36 scores.

**Abbreviations:** BDI-II, Beck Depression Inventory-II; BPI-I, Brief Pain Inventory-Interference; SF36, 36-item Short-Form Health Survey; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
were treated with 60 mg duloxetine once daily. In addition to constipation, somnolence, and dry mouth, other common (>5%) duloxetine-related AEs in the Chinese study included nausea, dizziness, decreased appetite, and insomnia. Somnolence and/or constipation were also common duloxetine-related AEs in two other randomized placebo-controlled trials conducted in North American and European patients with knee OA treated with 60–120 mg duloxetine once daily. Other duloxetine-related AEs in these trials included nausea, fatigue, dizziness, hyperhidrosis, and decreased libido. Similar incidence rates and types of AEs have also been observed in long-term studies of duloxetine in other chronic pain conditions, including in Japanese patients. In a 52-week extension study of duloxetine 60 mg in Japanese patients with fibromyalgia, the most common AEs considered treatment-related were somnolence (22.8%), constipation (18.1%), nausea (14.8%), weight increase (9.4%), dry mouth (7.4%), and malaise (5.4%). Most of these AEs occurred during the first 8 weeks of treatment. Similarly, in a 52-week

### Table 2 Changes in range of motion from baseline to the end of the extension study

<table>
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<th>Time point</th>
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<th>Double-blind phase group</th>
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<td>Baseline</td>
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<td>n</td>
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<tr>
<td>Median (range)</td>
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<tr>
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<tr>
<td>Mean (SD)</td>
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<td>127.6° (15.4°)</td>
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<td>Median (range)</td>
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<td>129.2° (16.1°)</td>
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</table>

**Abbreviation:** QD, quaque die (once daily).

### Table 3 Changes in KL grade from baseline to last observation

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<tr>
<td></td>
<td>Not measured</td>
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<tr>
<td>Double-blind phase group</td>
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<td></td>
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**Abbreviations:** KL, Kellgren–Lawrence; QD, quaque die (once daily).
Long-term treatment with duloxetine was not associated with substantial changes in ROM or KL grade. To our knowledge, this and the prior double-blind trial are the first studies to examine these parameters in patients with knee OA treated with oral pharmacotherapy, although changes in ROM have been studied previously in patients treated with intraarticular therapies, such as corticosteroids. The lack of ROM improvement in this study suggests that pain reduction may not be sufficient to increase joint mobility, and that additional therapy, such as exercise therapy, is required in conjunction with analgesia. Although an increase in daily activities made possible by pain reduction could potentially exacerbate knee OA, the lack of KL-grade worsening indicates that long-term treatment with duloxetine was not associated with worsening severity or progression of knee OA from a structural perspective. Further, despite being associated with radiographic progression of knee OA, KL grade changes slowly over time (compared with other joint disorders, such as rheumatoid arthritis) and differences may not be detectable, even after 52 weeks of treatment.

The strengths of this study include its extended duration (52 weeks) and the broad range of outcomes, including safety, efficacy (BPI-S average pain, WOMAC, PGI-I, CGI-I), and comprehensive measures of HRQoL (BPI-I, SF36), as well as the exploratory outcomes of KL grade and ROM. However, the study is limited by its open-label, single-treatment-arm design, the use of a single dose of duloxetine (60 mg), and the inclusion of only Japanese patients. Also, results from clinical trials are not always indicative of real-world results, as patients vary in their characteristics, levels of adherence, and comorbidities that may affect their response to duloxetine. For example, patients with depression were excluded from this study to observe the direct analgesic effects of duloxetine, rather than any potential pain reduction due to improvement in depressive symptoms.

**Conclusion**

In conclusion, long-term treatment with duloxetine was well tolerated in Japanese patients with knee OA and associated with sustained improvements in pain and comprehensive general and disease-specific HRQoL without any radiographic deterioration.

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Author contributions

All authors participated in the interpretation of study results, drafting, critical revision, and approval of the final version of the manuscript, and agree to be accountable for all aspects of the work. YU, MI, TO, and SK were involved in the study design and were investigators in the study. TT was an investigator in the study. TO was involved in the data collection and conducted the statistical analysis.

Disclosure

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References


Supplementary material

Table S1 Institutional review boards

Ethics Committee on Clinical Trial of Shionogi
Aino Clinic Institutional Review Board
Tokyo Midtown Clinic Institutional Review Board
Medical Corporation Eiyukai Yasuda Hospital Institutional Review Board
Sakayori Clinic Institutional Review Board
Sugiura Clinic Institutional Review Board
Onishi Medical Clinic Institutional Review Board
Maebashi Hirosegawa Clinic Institutional Review Board
Clinical Research Hospital Tokyo Institutional Review Board
Oita Central Institutional Review Board
Nakatani Hospital Institutional Review Board

Table S2 Baseline patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total n=93</th>
<th>Double-blind phase group</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo, n=50</td>
<td>Duloxetine 60 mg QD, n=43</td>
<td></td>
</tr>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>26 (28.0)</td>
<td>14 (28.0)</td>
<td>12 (27.9)</td>
</tr>
<tr>
<td>Female</td>
<td>67 (72.0)</td>
<td>36 (72.0)</td>
<td>31 (72.1)</td>
</tr>
<tr>
<td><strong>Age, mean (SD), years</strong></td>
<td>66.2 (8.2)</td>
<td>66.3 (8.7)</td>
<td>66.0 (7.7)</td>
</tr>
<tr>
<td><strong>Height, mean (SD), cm</strong></td>
<td>156.55 (8.91)</td>
<td>156.82 (8.89)</td>
<td>156.24 (9.03)</td>
</tr>
<tr>
<td><strong>Weight, mean (SD), kg</strong></td>
<td>63.78 (11.54)</td>
<td>62.73 (10.95)</td>
<td>65.01 (12.19)</td>
</tr>
<tr>
<td><strong>Use of NSAIDs in past 3 months, n (%)</strong></td>
<td>51 (54.8)</td>
<td>30 (60.0)</td>
<td>21 (48.8)</td>
</tr>
<tr>
<td><strong>Duration of OA, years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>4.8 (4.5)</td>
<td>5.1 (4.7)</td>
<td>4.4 (4.3)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>3.8 (0.3–20.8)</td>
<td>4.1 (0.4–20.8)</td>
<td>3.2 (0.3–18.8)</td>
</tr>
<tr>
<td><strong>BPI-S average pain score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>4.9 (1.0)</td>
<td>4.9 (1.0)</td>
<td>5.0 (1.0)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>5 (4–8)</td>
<td>5 (4–8)</td>
<td>5 (4–8)</td>
</tr>
<tr>
<td><strong>Concomitant medication, n (%)</strong></td>
<td>72 (77.4)</td>
<td>38 (76.0)</td>
<td>34 (79.1)</td>
</tr>
<tr>
<td>NSAIDs, acetaminophen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>89 (95.7)</td>
<td>47 (94.0)</td>
<td>42 (97.7)</td>
</tr>
<tr>
<td><strong>Combination therapy</strong></td>
<td>50 (53.8)</td>
<td>20 (40.0)</td>
<td>30 (69.8)</td>
</tr>
</tbody>
</table>

Notes: Use of NSAIDs for at least 14 days per month within the past 3 months before study start; nonpharmacological therapies used in combination with duloxetine.

Abbreviations: BPI-S, Brief Pain Inventory-Severity; NSAIDs, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; QD, quaque die (once daily).
Figure S1 Time course of change from baseline in WOMAC – (A) total, (B) pain, (C) stiffness, and (D) physical functioning scores.

Abbreviations: DBT, double-blind trial; EXT, extension; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
Figure S2 Time course of improvement in (A) PGI-I and (B) CGI-I scores.

Abbreviations: CGI-I, Clinical Global Impression-Improvement; DBT, double-blind trial; EXT, extension; PGI-I, Patient Global Impression-Improvement.