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RESEARCH ARTICLE

Evaluating the maintenance of effect of duloxetine in patients with diabetic peripheral neuropathic pain

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Abstract

Background To evaluate the maintenance of effect of duloxetine 60 mg QD over 26 weeks in patients with diabetic peripheral neuropathic pain (DPNP).

Methods Adult patients with DPNP and Brief Pain Inventory (BPI) 24-h average pain ≥4 were treated in this open-label study with duloxetine 60 mg QD for 8 weeks. Responders (≥30% pain reduction) continued on duloxetine 60 mg QD (maintenance arm) for 26 weeks while non-responders had duloxetine increased to 120 mg QD (rescue arm). The primary outcome measure was the mean change from baseline (Week 8) to endpoint (Week 34) in BPI average pain in the maintenance arm. A number of secondary efficacy measures, as well as safety and tolerability, were assessed.

Results Two hundred and sixteen patients entered the study and their baseline BPI average pain was 5.9. Thirty-two patients (15%) discontinued during the acute phase. One hundred and fifteen (53%) patients were found to be responders to 60 mg dose and they entered the maintenance arm. During the maintenance period they reported a mean change of BPI average pain of 0.35, with 0.79 as the upper bound of the one-sided 97.5% CI, which was less than the pre-specified non-inferiority margin of 1.5 ($p < 0.001$). Non-responders, upon dose increase to 120 mg QD, reported a statistically significant pain reduction. Total of 119 patients completed either arm of the study. Twenty patients experienced 27 serious adverse events including one death.

Conclusion In this open-label study, the effect of duloxetine 60 mg QD in patients with DPNP was maintained over 6-month period. Copyright © 2009 John Wiley & Sons, Ltd.

Keywords duloxetine; maintenance of effect; diabetic peripheral neuropathic pain

Introduction

Diabetic peripheral neuropathy is a chronic complication of diabetes mellitus typically occurring after prolonged periods of sub-optimal glycaemic control and its pathophysiology has been reviewed [1]. Diabetic peripheral neuropathy is commonly associated with chronic pain of variable severity. The pain is often described as an 'aching, burning, stabbing, or tingling' sensation, and often it affects sleep and mood [2,3].

In pathological pain states, the endogenous pain inhibitory mechanisms both in the brain and the spinal cord mediated by serotonin (5-HT) and noradrenaline were shown to be dysfunctional [4,5]. Impairment in these inhibitory mechanisms may be a part of the central sensitization of the pain transmitting pathways contributing to the manifestation of chronic pain [6]. Tricyclic anti-depressants (TCAs) are widely used to treat pain as these compounds are known to modulate 5-HT and noradrenaline systems [7,8]. The TCAs seem to provide benefit to patients with painful diabetic neuropathy [7] and other chronic pain conditions [8,9]. However, TCAs as a class are burdened by many side effects likely related to their considerable affinity for a number of different neuronal receptors [10]. Duloxetine, a selective 5-HT and noradrenaline reuptake inhibitor, has been shown to be effective in four distinct chronic pain conditions: diabetic peripheral neuropathic pain (DPNP) [11–13], fibromyalgia [14–16], osteoarthritis pain [17], and chronic low back pain [18]. Its safety and tolerability profile also appears to be favourable as compared to TCAs [19,20].

All previous efficacy studies of duloxetine in DPNP were of 12 weeks' duration. In clinical practice, however, patients typically require prolonged treatment with an analgesic agent.

This study was designed to investigate the maintenance of effect of duloxetine 60 mg once daily (QD) over 26 weeks in patients who responded to the initial 8 weeks of acute therapy. Patients who did not respond to duloxetine 60 mg QD during the acute therapy phase had their dose of duloxetine increased to 120 mg QD for up to 26 weeks in order to observe for a response at the higher dose. In this manuscript, we report on the long-term efficacy and safety of duloxetine 60 and 120 mg QD in patients with DPNP.

Materials and methods

Study design

This was an open-label multi-centre study with four study periods (Figure 1). Study Period I, during which patients were screened for study eligibility, was approximately 1-week long. Patients who met entry criteria were started on duloxetine 30 mg QD for 1 week, followed by duloxetine 60 mg QD for additional 7 weeks (Study Period II, Weeks 0–8). Study Period III (Weeks 8–34) was an open label either maintenance or rescue therapy arm of approximately 26 weeks' duration. At the beginning of Study Period III, patients whose Brief Pain Inventory (BPI) average pain rating had decreased by ≥30% from Week 0 (responders) continued on duloxetine 60 mg QD (maintenance arm). Patients who did not achieve a ≥30% reduction (non-responders) from Week 0 on the BPI average pain rating had their dose of duloxetine increased to 120 mg QD at Week 8 (rescue arm). At each visit, using the Patient's Global Impressions of Improvement (PGI-I) and the Clinical Global Impressions of severity (CGI-S) scales, patients in the maintenance arm were assessed for their continued eligibility to remain in that cohort. If a patient's CGI-S and PGI-I ratings at any visit from Week 12 to 24 were both ≥4 and represented an increase of at least 1 from the rating at Week 8, the duloxetine dose was increased to 120 mg QD and the patient was moved to the rescue arm. Patients' response calculations and dose adjustments were performed by an interactive voice response system. Patients who did not tolerate duloxetine during any of the above three study phases were discontinued. Patients who completed the treatment and non-tolerant patients who took duloxetine for at least 7 days were entered into Study Period IV, which was a 2-week tapering period leading to duloxetine discontinuation.

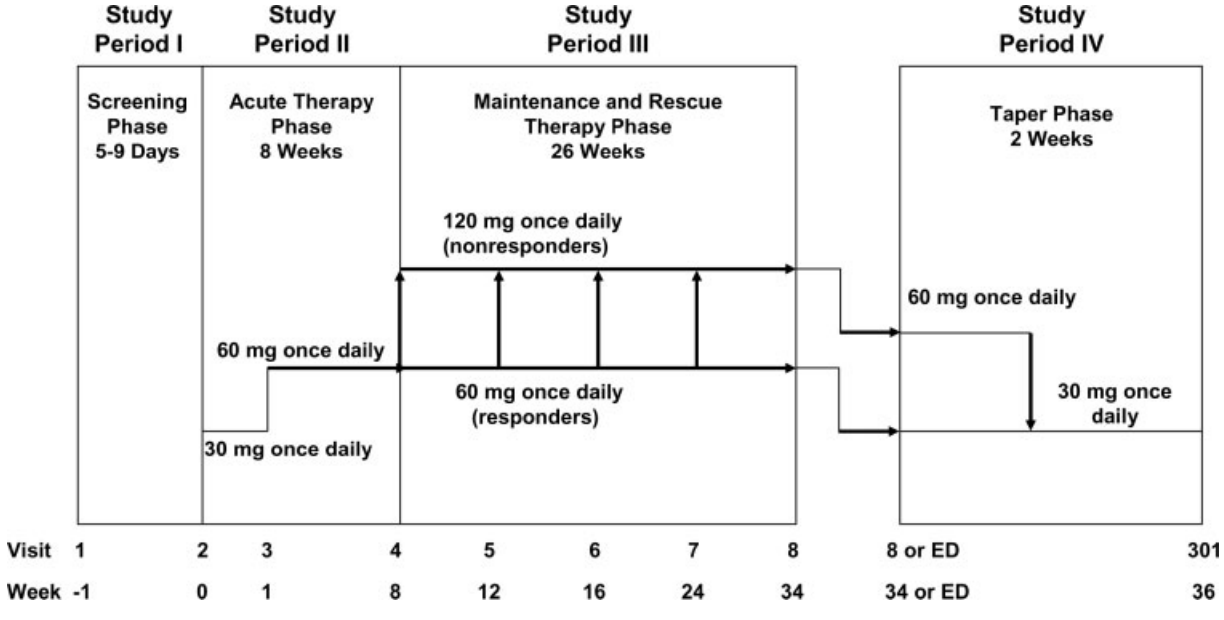

Figure 1. Study design showing all four study periods

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This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and its guidelines on good clinical practices. The Ethical Review Boards at each investigational site provided written approval of the study protocol and the informed consent document. No protocol-related procedures were performed prior to patients signing the informed consent document.

Patients

Male or female outpatients ≥18 years of age who presented with pain due to diabetic peripheral neuropathy and had a rating of ≥4 on the BPI 24-h average pain item (hereafter referred to as BPI average pain) were included in this study [21]. Patients must have had daily pain for at least 6 months prior to entry in the study and the pain must have begun in the feet with relatively symmetrical onset. The disease diagnosis was confirmed by a score of at least 3 on the clinical portion of the Michigan Neuropathy Screening Instrument (MNSI) [22]. Although MNSI score of ≥2 was found to be associated with diagnosis of DPN in 28 out of 29 patients in a single-centre study [22], for the purpose of this multi-centre trial a score of >3 was used instead. One patient with the MNSI score of 2 was inadvertently entered into the study. This patient was identified as protocol violation. However, following the principle of intent-to-treat analysis that patient was included in all analyses.

Patients with unstable glycaemic control (glycosylated haemoglobin >12%), and/or any medical or other condition that could compromise participation were excluded. Patients were also excluded from the study if judged by the clinical investigator to be at suicidal risk or if they had a rating of 2 or greater on question 9 of the Beck Depression Inventory-II [23]. During the study, concomitant use of anti-depressants, anti-convulsants, opioids, and other analgesic drugs, as well as drugs that interfere with the metabolism of duloxetine, was not allowed. The exceptions to the above rule were (1) an episodic use of paracetamol at doses up to 4000 mg per day as rescue therapy for DPNP and (2) an episodic use of any short-term analgesic for acute injury, surgery or conditions unrelated to DPNP. Episodic use was defined as no more than 3 consecutive days and not to exceed 40 total days during the study.

Treatment

Study medication was provided in capsules containing either 30 or 60 mg of duloxetine hydrochloride as enteric-coated pellets. Throughout the study, patients took one or two capsules in the morning following the regimen described in the study design section.

Efficacy measures

The primary objective of the study was to evaluate the maintenance of effect of duloxetine 60 mg QD in patients who had achieved at least a 30% pain reduction from baseline after 8 weeks of initial acute treatment. The primary outcome measure was the BPI average pain rating, which is a self-reported numerical scale rating the pain severity over the previous 24 h. It ranges from 0 (no pain) to 10 (pain as bad as you can imagine).

The secondary efficacy outcome measures assessed in this study were: percentage of patients with a ≥50% reduction on BPI 24-h average pain (to measure the response to treatment in both maintenance and rescue arms); BPI-severity (BPI-S) and BPI-interference (BPI-I) [21] (for assessment of the severity of pain and its interference with function); the PGI-I [24] (to measure the patients' perceived change in overall well-being); and the CGI-S (to assess clinician's rating of the illness severity) [24]; the sensory portion of the Short-Form McGill Pain Questionnaire(SF-MPQ SS) [25] (to assess the quality of pain).

Safety measures

During the study, adverse events were recorded at every visit, regardless of their perceived relationship to study drug. These events were captured as actual verbatim terms and coded to Medical Dictionary for Regulatory Activities terms (MedDRA) by Lilly medical personnel. Vital signs, including blood pressure (systolic and diastolic), pulse rate, and weight, were collected at all scheduled study visits.

Statistical analyses

The primary efficacy analysis was to test the null hypothesis that duloxetine treatment effect on pain reduction on DPNP patients is not maintained in the 26-week maintenance phase. The null hypothesis was tested by a non-inferiority test evaluating a one-sided 97.5% confidence interval (CI) of the change from baseline to endpoint on the BPI average pain rating. When the upper bound of the one-sided 97.5% CI was less than or equal to the pre-specified non-inferiority margin of 1.5 points on the BPI pain scale, the null hypothesis was rejected at the significance level of 0.025. The margin of 1.5 points on the BPI average pain scale was established based on studies of minimal clinically important difference in pain ratings [26,27]. In this analysis, baseline was defined as the observation at Visit 4 (Week 8), and endpoint was defined as the last non-missing observation [last-observation-carried-forward (LOCF)] during Weeks 12–34 while patients were on duloxetine 60 mg QD.

The study planned to enrol 212 patients so as to have at least 80% probability that the upper limit of the one-sided 97.5% CI would not exceed 1.5. The sample size was determined using a one-sided non-inferiority test with a type I error of 0.025 and a margin of 1.5 points on the BPI pain scale, and assuming the mean change of the BPI 24-h average pain of 0.7 during the 26-week maintenance therapy phase, standard deviation of

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the change of 2.6, 55% of the patients meeting entry criteria for the maintenance phase, and discontinuation rates of 22% and 45% for the acute therapy phase and maintenance therapy phase, respectively, which is similar to those observed in acute placebo-controlled as well as open-label duloxetine studies [11,13,19,20].

All analyses were conducted on an intent-to-treat basis, meaning that data were analysed for all patients meeting criteria to enter the acute, maintenance or rescue therapy phase, even if the patient did not take the assigned treatment, did not receive the correct treatment, or did not comply with the protocol. The maintenance arm (Study Period III) was the major focus of efficacy analyses, while the data from the acute phase (Study Period II) and the rescue arm (Study Period III) were also analysed. For the analyses of acute phase, baseline was defined as the LOCF at Visit 2 (Week 0), and endpoint was defined as the LOCF during Weeks 3–4. For the analyses of rescue arm, baseline was defined as the observation at Visit 4 (Week 8), and endpoint was defined as the LOCF during Weeks 12–34 while patients were on duloxetine 120 mg QD. When an average score was computed from individual items, it was calculated from non-missing values. For analyses regarding both efficacy and safety variables, a Student's *t* test was used to test the within-group change from baseline to endpoint, unless the assumption of a *t* test appeared to be violated, in which case the Wilcoxon signed-rank procedure was used. Comparison was not made between different duloxetine dose groups. Statistical significance was evaluated at the level of 0.05 unless otherwise specified. Statistical Analysis Software (SAS, version 9.1) was used to perform all statistical analyses in this study.

At study endpoint (Week 34), the number of patients achieving 50% pain reduction on BPI average pain was calculated relative to baseline (Week 0) for patients who entered the maintenance treatment arm and for those who entered the rescue treatment arm.

As pre-specified in the protocol, safety analyses were conducted separately for the duloxetine 60 mg group and the 120 mg group across the entire study. For the duloxetine 60 mg group, the baseline visit interval was Visit 1–2 (Week −1 to 0), and the endpoint visit interval was Visit 3 (Week 1) through to the visit where patients received the last dose of 60 mg. For the duloxetine 120 mg group, the baseline visit interval included acute phase visits and the visits at maintenance arm where patients were on 60 mg, in other words, Visit 3 (Week 1) to the visit where patients received the last dose of 60 mg; the endpoint visit interval was the visits where patients were on 120 mg, in other words, the first visit on a dose of 120 mg to Visit 8 (Week 34).

Patients who entered the duloxetine 120 mg rescue therapy phase at Visit 5, 6, or 7 on duloxetine 60 mg were pooled with patients who remained on duloxetine 60 mg throughout Study Period III, and patients on duloxetine 120 mg were pooled with patients who entered the duloxetine 120 mg rescue therapy phase at Visit 4.

Results

The study was conducted at 21 sites in Brazil, France, Germany, and Italy by physicians specialized in endocrinology, internal medicine, neurology, pain management, or psychiatry. The trial began on 27 April 2006 and ended on 30 October 2007.

Patient disposition, demographics, disease characteristics, and concomitant medications

Of the 216 patients enrolled, 184 patients receiving duloxetine 60 mg QD completed the 8-week acute treatment period. Of these, 103 patients continued in the maintenance treatment arm and stayed on duloxetine 60 mg QD, while 69 patients proceeded with the rescue treatment arm receiving duloxetine 120 mg QD. A total of 77 and 33 patients completed the study in the maintenance and rescue treatment arms, respectively. In addition, 12 patients who began the maintenance arm had their dose of duloxetine increased to 120 mg QD at either Week 12, 16, or 24. Nine of these patients completed the rescue treatment arm (Figure 2).

The baseline demographics and disease characteristics of the patients entered into the study are shown in Table 1. For patients in the maintenance and rescue treatment arms, the baseline characteristics were similar.

Overall, out of 216 study participants, 17 (7.9%) of them reported use of paracetamol at any time; 11 (9.6%) patients in the maintenance arm (receiving duloxetine 60 mg QD) reported use of paracetamol during that phase of the study. The corresponding number of patients in the rescue arm (receiving duloxetine 120 mg QD) was 6 (8.7%).

Efficacy of duloxetine

Maintenance arm (responders)

A total of 115 patients, or 53.2% of all enrolled patients, were determined to be responders (≥30% pain reduction) at the end of Week 8 and entered the maintenance arm.

The primary outcome measure was the mean change in BPI average pain from the post-acute phase baseline (Week 8) to the endpoint (the LOCF during Weeks 12–34 while taking duloxetine 60 mg QD) of the maintenance treatment arm. The maintenance of effect was tested using a one-sided 97.5% CI of the change from baseline to endpoint on BPI average pain as discussed in the "Materials and methods" section. The mean change from baseline to endpoint was 0.35, with 0.79 as the upper limit of the 97.5% CI. With the upper limit of the CI being below the pre-specified non-inferiority margin of 1.5, the maintenance of effect of duloxetine on pain reduction in patients with DPNP was confirmed.

The results of the analysis of the least square mean changes in the BPI average pain ratings over time among

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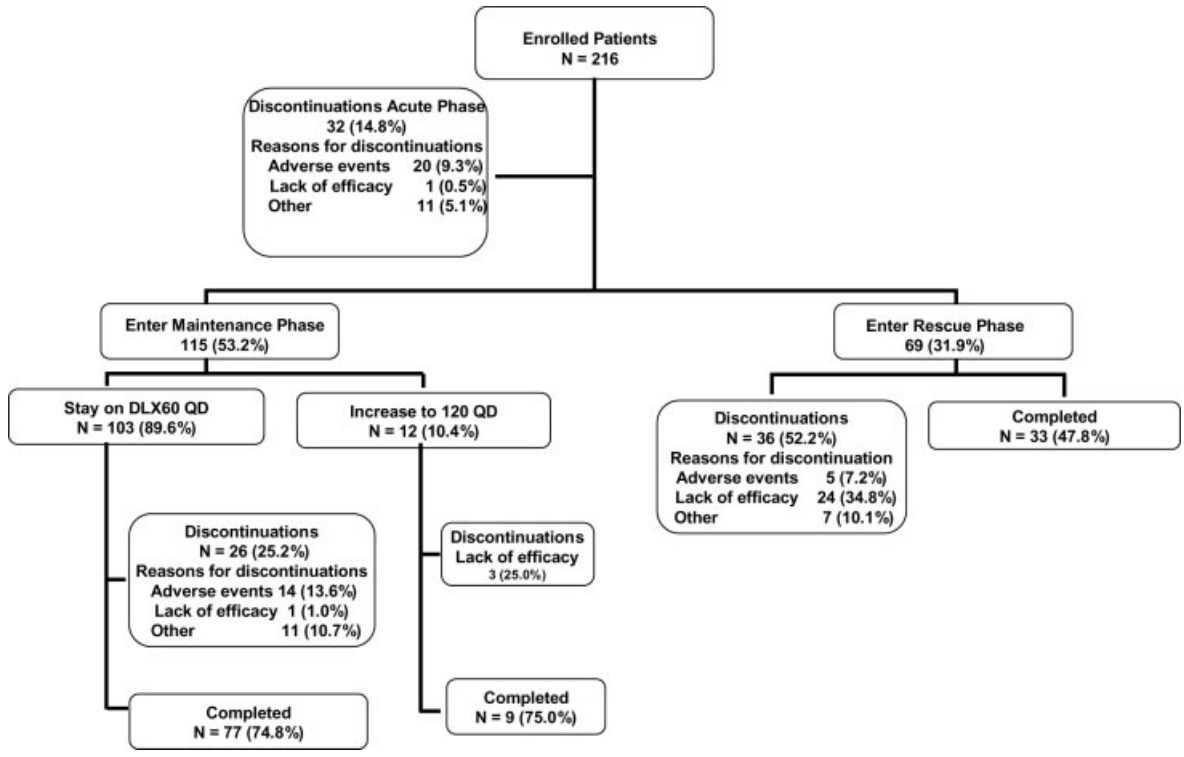

Figure 2. Patient disposition

Table 1. Baseline demographics and disease characteristics in patients treated with duloxetine in the acute, maintenance, and rescue treatment arms

	Duloxetine		
	Acute (8 weeks) $N = 216$	Responders (maintenance) $N = 115$	Non-responders (rescue) $N = 69$
Age, years, mean (SD)	63.3 (9.5)	62.6 (9.4)	63.5 (9.1)
Origin, *n* (%)			
Caucasian	173 (80.1)	85 (73.9)	58 (84.1)
West Asian	33 (15.3)	24 (20.9)	8 (11.6)
Other	10 (4.6)	6 (5.2)	3 (4.3)
Gender, *n* (%)			
Male	112 (51.9)	58 (50.4)	34 (49.3)
Weight, kilogram, mean (SD)	84.0 (18.4)	83.3 (17.3)	83.2 (20.7)
Type 2 diabetes, *n* (%)	204 (94.4)	110 (95.7)	66 (95.7)
Duration of diabetes, years, mean (SD)	14.4 (9.7)	14.7 (9.7)	12.9 (8.9)
Duration of DPNP, years, mean (SD)	4.2 (4.0)	4.5 (4.4)	3.7 (3.5)
MNSI score, mean (SD)	5.3 (1.3)	5.4 (1.3)	5.2 (1.3)
BPI average pain, mean (SD)	5.9 (1.5)	6.0 (1.4)	5.7 (1.3)
CGI-S, mean (SD)	3.8 (1.2)	3.8 (1.1)	3.8 (1.2)
PGI-S, mean (SD)	3.8 (1.3)	3.8 (1.3)	3.9 (1.2)
SF-MPQ SS, mean (SD)	16.2 (7.4)	6.5 (5.9)	13.6 (6.7)
Haemoglobin A1c, mean (SD)	0.08 (0.01)	0.08 (0.01)	0.08 (0.01)

BPI, Brief Pain Inventory; CGI-S, Clinical Global Impressions of severity; DPNP, diabetic peripheral neuropathic pain; MNSI, Michigan Neuropathy Screening Instrument; PGI-S, Patient's Global Impressions of severity; SD, standard deviation; SF-MPQ SS, Sensory portion of Short-Form McGill Pain Questionnaire.

patients in the maintenance treatment arm are shown in Figure 3. The mean pain ratings increased by 1.04 ± 0.24 points at Week 12 ($p < 0.001$) and 0.49 ± 0.20 points at Week 16 ($p = 0.017$) relative to Week 8, followed by a return to the post-acute phase baseline level for the remainder of the study (Weeks 24 and 34).

Most of the secondary efficacy measures in the maintenance treatment arm did not change significantly from the post-acute phase baseline, further indicating the maintenance of effect among duloxetine responders. The BPI-S item 'pain right now' and the BPI-I item 'normal work' were the only 2 out of the 15 secondary outcome measures which significantly changed (worsened) during the 26-week maintenance therapy phase (Table 2).

Of the 114 patients with baseline and at least one non-missing post-baseline BPI average pain rating receiving

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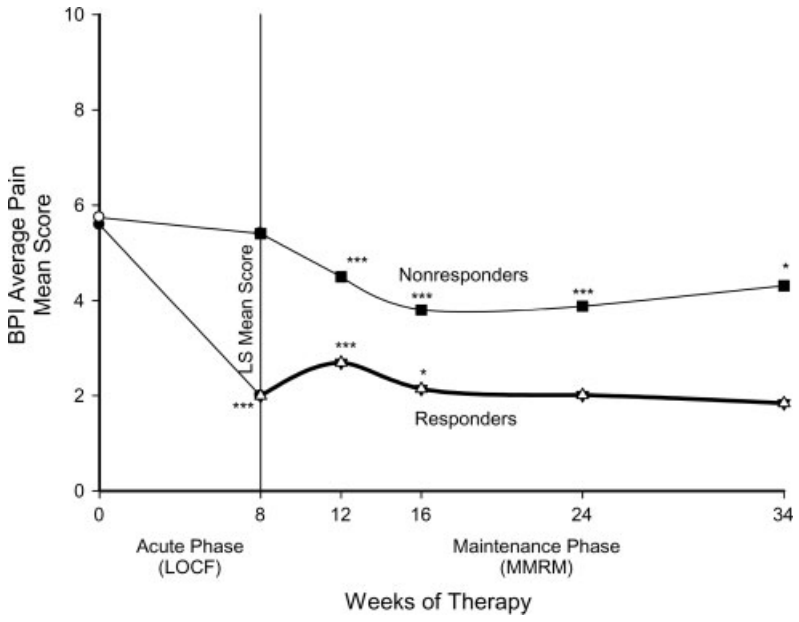

Figure 3. Brief Pain Inventory (BPI) average pain over time in the acute (LOCF = Last-observation-carried-forward), maintenance, and rescue treatment arms (MMRM = mixed model repeated measures). *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$ from respective baseline values. The bolded line (responders) in the graph represents the primary efficacy measure

Table 2. Secondary efficacy measures in the acute, maintenance, and rescue treatment arms

	Acute (8 weeks)	Responders (maintenance)	Non-responders (rescue)
BPI-severity			
Average pain	−2.49[a]	0.35	−1.39[a]
Worst pain	−2.90[a]	0.29	−1.33[a]
Least pain	−1.73[a]	0.24	−0.93[b]
Pain right now	−2.20[a]	0.48[b]	−1.12[b]
BPI-interference			
Average interference	−2.52[a]	0.28	−0.59
General activity	−2.45[a]	0.22	−1.01[b]
Mood	−2.59[a]	0.39	−0.29
Walking ability	−2.60[a]	0.59	−1.15[c]
Normal work	−2.57[a]	0.63[b]	−0.97[b]
Relations with other people	−2.04[a]	0.13	−0.12
Sleep	−2.72[a]	−0.10	−0.84
Enjoyment of life	−2.59[a]	0.11	0.19
PGI-I	–	2.32	3.04
CGI-S	−0.96[a]	−0.11	−0.46[c]
SF-MPQ SS	−6.43[a]	0.31	−1.38
50% Response rates on BPI average pain, *n* (%)	–	76 (66.7)	21 (31.8)

Values are mean change from baseline to endpoint analysed by last-observation-carried-forward approach. Sample sizes varied for each measure and included patients with a baseline and at least one non-missing post-baseline value.
BPI, Brief Pain Inventory; CGI-S, Clinical Global Impressions of severity; PGI-I, Patient's Global Impressions of Improvement; SF-MPQ SS, Sensory portion of Short-Form McGill Pain Questionnaire.
[a]$p \leq 0.001$ from respective baseline values.
[b]$p \leq 0.01$ from respective baseline values.
[c]$p \leq 0.05$ from respective baseline values.

duloxetine 60 mg QD in the maintenance treatment arm, 76 (66.7%) of them had at least 50% pain reduction relative to Week 0, as measured by the BPI average pain ratings (Table 2).

Twelve patients in the maintenance arm who were responders at the end of Week 8 had to have their dose of duloxetine increased to 120 mg QD at Weeks 12, 16, or 24, because of a decline in therapeutic response as described in the "Study design" section. In this group of patients, the only efficacy measures that significantly improved from baseline (Week 8) at endpoint (Week 34) were the CGI-S (mean change, −1.50, $p \leq 0.001$) and walking ability (mean change, −2.08, $p = 0.013$) and sleep (mean change, −2.33, $p = 0.020$) items on the BPI-I.

Rescue treatment arm (non-responders)

Sixty-nine (31.9%) patients had less than 30% pain reduction by the end of Week 8. They represent the

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non-responder cohort which, at that point, had their individual doses of duloxetine increased to 120 mg QD for the remainder of the study.

The least square mean changes in the BPI average pain ratings over time among patients in the rescue treatment arm are shown in Figure 3. In the rescue treatment arm, relative to the post-acute phase baseline (Week 8), pain ratings were statistically significantly reduced at all time points ($p \leq 0.001$) and at Week 34 ($p \leq 0.05$). The range of improvement was -1.02 ± 0.24 (at Week 12) to -1.72 ± 0.27 (at Week 16).

Similar to the improvement observed using BPI average pain ratings, patients in the rescue treatment (non-responders) arm showed significant improvement at endpoint (Week 34) relative to baseline (Week 8) in both CGI and PGI ratings, as well as on all four items of the BPI-S. Of the 66 patients with baseline and at least one non-missing post-baseline BPI average pain rating receiving 120 mg QD in the rescue treatment arm, 21 (31.8%) had at least 50% pain reduction from Week 8 on the BPI average pain item. Table 2 provides overview of all secondary endpoints pertinent to the rescue treatment arm.

Acute treatment arm

The BPI average pain ratings of the raw mean values among patients in the acute treatment arm are shown in Figure 3. The pain ratings were significantly ($p \leq 0.001$) reduced from baseline (Week 0) to endpoint (LOCF) (Week 8). The absolute mean (SD) change from baseline to endpoint was −2.49 (2.37).

The BPI-S and BPI-I items, PGI-I, CGI-S, and SF-MPQ SS all significantly improved from baseline (Week 0) to endpoint (Week 8) (LOCF) in patients receiving duloxetine 60 mg QD in the acute treatment arm ($p \leq 0.001$) (Table 2).

Safety and tolerability

Overall, 20 (9.3%) patients experienced a total of 27 serious adverse events during the entire study period (Table 3). One sudden death occurred in the duloxetine 60 mg QD group at day 109 of the study. This was a 55-year-old male patient with a medical history that included type 2 diabetes mellitus and smoking up to 10 years prior to the study. The patient had elevated triglycerides and a family history of cardiopathy. The death was suspected to be because of an asymptomatic cardiac event. No autopsy was performed and the cause of death was deemed indeterminate, but was not thought to be study-drug related in the judgement of the investigator. The most common reason for discontinuation from the study during the acute treatment phase and for patients remaining on duloxetine 60 mg QD in the maintenance treatment phase was adverse events [20 (9.3%) and 14 (13.6%) patients, respectively]. For patients who entered the rescue treatment phase at the dose of 120 mg QD and for patients who increased to 120 mg QD during the maintenance phase, the most common reason for discontinuation was lack of efficacy [24 (34.8%) and 3 (25.0%) patients, respectively].

Table 3. Serious adverse events occurring by decreasing frequency in all randomized patients

Preferred term	Duloxetine $N = 216$ n (%)	
Patients with ≥1 serious adverse event	20	(9.3)
Cataract	2	(0.9)
Chest pain	2	(0.9)
Angina unstable	1	(0.5)
Anuria	1	(0.5)
Atrial fibrillation	1	(0.5)
Breast cancer	1	(0.5)
Cardiac failure congestive	1	(0.5)
Cholelithiasis	1	(0.5)
Diabetes mellitus	1	(0.5)
Diabetic ketoacidosis	1	(0.5)
Diabetic neuropathic ulcer	1	(0.5)
Dyspnoea	1	(0.5)
Hyperthyroidism	1	(0.5)
Hypokalaemia	1	(0.5)
Intestinal ischaemia	1	(0.5)
Oesophageal ulcer haemorrhage	1	(0.5)
Peripheral arterial occlusive disease	1	(0.5)
Pruritus	1	(0.5)
Rib fracture	1	(0.5)
Sudden death	1	(0.5)
Suicidal ideation	1	(0.5)
Syncope	1	(0.5)
Transient ischaemic attack	1	(0.5)
Urinary retention	1	(0.5)
Viral labyrinthitis	1	(0.5)

Of the 216 patients who received duloxetine 60 mg QD during the study, 139 (64.4%) reported at least one treatment-emergent adverse events (TEAE). For the 81 patients who received duloxetine 120 mg QD during the study, TEAEs were reported by 39 (48.1%) patients. Most commonly reported TEAEs, occurring at rate ≥5%, are shown in Table 4.

Patients in the duloxetine 60 mg QD group experienced statistically significant ($p \leq 0.001$) decreases from baseline to endpoint in systolic blood pressure (−4.24 mm

Table 4. Treatment-emergent adverse events occurring at rate ≥5%

Event	Duloxetine 60 mg QD $N = 216$ n (%)		Duloxetine 120 mg QD $N = 81$ n (%)	
Nausea	41	(19.0)	1	(1.2)
Somnolence	18	(8.3)	1	(1.2)
Hyperhidrosis	14	(6.5)	1	(1.2)
Dry mouth	13	(6.0)	1	(1.2)
Anorexia	12	(5.6)	0	(0.0)
Asthenia	11	(5.1)	1	(1.2)
Fatigue	11	(5.1)	0	(0.0)
Headache	11	(5.1)	3	(3.7)
Diarrhoea	7	(3.2)	7	(8.6)

For 60 mg group, baseline: Visit 1 (Week −1) to Visit 2 (Week 0); endpoint: Visit 3 (Week 1) through the last dose of 60 mg. For 120 mg group, baseline: Visit 3 (Week 1) through the last dose of 60 mg; endpoint: the first visit on 120 mg to Visit 8 (Week 34).

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Hg) and weight (−1.29 kg), and a statistically significant ($p \leq 0.001$) increase in heart rate (2.39 bpm). There were no significant changes in vital signs from baseline to endpoint in the duloxetine 120 mg QD treatment group.

Discussion

This open-label uncontrolled trial demonstrated the maintenance of effect of duloxetine 60 mg QD over a period of 26 weeks in patients with DPNP who responded to the initial 8 weeks of acute therapy. The maintenance of effect was assessed using the group mean change of BPI average pain as the primary outcome measure and the non-inferiority test with an *a priori*-specified margin of $\Delta 1.5$ and one-sided 97.5% CI. Improvement in some of the secondary efficacy measures pertinent to the responders' cohort, particularly PGI-I, further supports the maintenance of effect of duloxetine in the treatment of DPNP over time. The transient increase in pain ratings observed at Weeks 12 and 16, although statistically significant, can hardly be seen as significant clinically since it corresponds to a pain increase of 1.04 ± 0.24 points at Week 12 and 0.49 ± 0.20 points at Week 16 relative to baseline. The aetiology of this transient phenomenon is unclear. The fact that it occurs immediately following the critical point of efficacy assessment at Week 8 may imply relatedness of the pain increase to the open-label study design.

At least a 50% pain reduction on the BPI average pain item in 66.7% of the patients receiving duloxetine 60 mg QD in the maintenance arm and 31.8% of the patients in the non-responders receiving 120 mg QD in the rescue arm is noteworthy, as a 30% pain reduction is considered to be clinically significant [26].

The amount of pain reduction observed during the acute treatment period and maintained through the maintenance treatment period is comparable to that seen in placebo-controlled studies [11,13,19,20], indicating consistency of duloxetine therapeutic response. An important characteristic of this study is the flexibility of the dosing regimen, which reflects common clinical practice where a higher dose is given only to patients with a sub-optimal response to a lower dose. The findings from the rescue (non-responder) treatment arm suggest that duloxetine at the dose of 120 mg per day provides an additional 10% of patients with a clinically very significant pain reduction of 50%.

The safety profile of duloxetine in this long-term study is consistent with the findings of previous studies [13,19,20]. A total of 27 serious adverse events were experienced only in 9.3% of patients. Similarly, 9.3%, 13.6%, and 7.2% of patients discontinued due to adverse events in the acute, maintenance, and rescue treatment arms, respectively. In general, duloxetine was safe and well tolerated during the 26-week maintenance period. Similar or slightly higher percentages of patients discontinued due to adverse events in other chronic pain studies with duloxetine including fibromyalgia [14–16], osteoarthritis knee pain [17], and chronic low back pain [18].

Sixty-four percent of patients receiving duloxetine 60 mg QD from baseline to the end of maintenance period had at least one TEAE, and these patients frequently reported nausea, somnolence, hyperhidrosis, and dry mouth. These findings are consistent with those reported by patients in other chronic pain conditions treated with duloxetine [13–20].

Consistent with its noradrenergic activity, duloxetine slightly increased the heart rate from baseline to endpoint but the increase was, in general, not considered clinically significant.

As with any open-label uncontrolled study, this study's findings should be interpreted cautiously, as the lack of blinding may have introduced a bias in evaluation of endpoints and of the safety profile. However, since a placebo-controlled study of this duration is unethical, this study likely provides the best possible evidence of the maintenance of effect of duloxetine at therapeutic dose over a period of 26 weeks in patients with DPNP.

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Conflict of interest

Drs Skljarevski, Desaiah, Zhang, Chappell, and Detke are or were employees and stockholders of Eli Lilly and Company. Dr Gross was the principal investigator and was funded by Eli Lilly and Company for conducting this study. Dr Ziegler is a scientific advisor to Eli Lilly and Company and has helped design the study and interpret its results.

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