Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Report date: 09 NOV 2006	**Number:** U06-2101	**Study period (dates):** 3 MAY 05 - 02 MAY 06		

Title of study:	A ten-week, randomized, double-blind study evaluating the efficacy of duloxetine 60 mg once daily versus placebo in outpatients with major depressive disorder and pain (**EU-Pain enriched study**)
Investigator:	[redacted]
Study centres:	Multi-centre study, 38 sites in 5 European countries, refer to Appendix 16.1.4
Publication (reference):	Data of this study have not been published.
Clinical phase:	IIIb
Objectives:	The purpose of this study was to investigate the efficacy of duloxetine versus placebo on pain in outpatients with major depressive disorder (MDD): change in Brief Pain Inventory Short Form (BPI-SF) 24-hour average pain score from baseline over the 8 weeks of treatment.
Methodology:	Randomized, placebo-controlled, double-blind, fixed dose, multi-centre trial with 10 weeks of treatment (a 1-week escalation phase followed by 7 weeks of 60 mg duloxetine p.o. per day and a 2-week tapering phase)
No. of subjects:	
planned:	entered: 310
actual:	enrolled: 393 entered: 327 Placebo (PBO): entered: 165 treated: 165 analysed (for primary endpoint): 159 Duloxetine (DLX): entered: 162 treated: 162 analysed (for primary endpoint): 156
Diagnosis and main criteria for inclusion:	Patients ≥18 years old, with MDD according to DSM-IV criteria and confirmed by mini international neuropsychiatric interview (MINI); with at least one previous depressive episode; total score on the Montgomery-Asberg Depression Rating Scale (MADRS) ≥20; a score ≥3 for the average pain item of the BPI-SF; clinical global impressions (CGI) severity score ≥4.
Test product:	Duloxetine capsules
dose:	2 x 30 mg daily (main phase), 1 x 30 mg daily (escalation and tapering phase)
mode of admin.:	Orally (p.o.)
batch no.:	CT516992

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Duration of treatment:	Double-blind dose escalation with 30 mg duloxetine (or placebo): 1 week Double-blind treatment with 60 mg duloxetine (or placebo): 7 weeks Double-blind tapering with 30 mg duloxetine (or placebo): 2 weeks Total: 10-week double-blind treatment
Reference therapy:	Placebo
dose:	Not applicable
mode of admin.:	Orally (p.o.)
batch no.:	CT509251
Criteria for evaluation:	
Efficacy:	Primary efficacy endpoint: Change in the score for item 5 (average pain of the last 24 hours) of the BPI-SF for duloxetine versus placebo from baseline over 8 weeks of treatment with 60 mg duloxetine (or placebo). Secondary efficacy criteria: MADRS total score, other BPI-SF items, SCL-90R, CGI-severity, CGI-improvement, PGI-improvement.
Safety:	Vital signs, treatment-emergent adverse events, treatment discontinuation-emergent adverse events, routine laboratory tests.
Statistical methods:	Analysis method for primary endpoint: Mixed effect model repeated measures (MMRM); power: 80% for question 5 of BPI-SF and 85% for MADRS; delta: 0.8 (SD 2.5) for question 5 of the BPI-SF and 2.0 (SD 5.8) for MADRS; alpha-level: 0.05, two-sided.
SUMMARY – CONCLUSIONS:	
Efficacy results:	In total, 73.7% of the patients were female. The mean age was 50.2 years. On average, patients were 39 years old at the time of their first depressive episode. The mean baseline score for the BPI-SF average pain was 5.7 in both groups, whereas the MADRS total score was 29.2 (PBO) and 29.9 (DLX). There were no relevant between-group differences for baseline parameters. For the BPI-SF average pain score, adjusted mean changes from baseline at Week 8 were −1.64 (PBO) and −2.57 (DLX) with a p-value for the treatment difference of 0.0008. The p-value for the treatment-by-time interaction was 0.0468, indicating a treatment-specific response over time. Sensitivity analysis by ANCOVA confirmed the favourable results for duloxetine. Almost all secondary endpoints revealed beneficial effects of duloxetine versus placebo. At Week 8, 44.03% of the placebo patients and 60.26% of the duloxetine patients were responders for the BPI-SF average pain score (at least

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Efficacy results: (continued)

30%-reduction of the score from baseline); p=0.0045. The time to sustained response for the BPI-SF average pain score was substantially shorter for duloxetine than for placebo (Kaplan-Meier survival analysis and log rank test; p=0.0010). After 8 weeks of treatment, the adjusted mean changes from baseline for the AUC of the BPI-SF average pain score were −70.12 (PBO) and −87.73 (DLX). The adjusted mean difference from placebo was −17.61 in favour of duloxetine (p=0.0839).

At Week 8, the adjusted mean changes from baseline for the MADRS total score were −11.31 (PBO) and −16.69 (DLX) with a p-value for the treatment difference of <0.0001. The p-value (MMRM analysis) for the treatment-by-time interaction was 0.0001. The proportion of MADRS responders (reduction of the total score from baseline of at least 50%) at Week 8 was 35.22% (PBO) and 55.13% (DLX) with a p-value of 0.0003. Kaplan-Meier survival analysis and log rank test revealed a substantially shorter time to sustained response for the MADRS total score in the duloxetine group than in the placebo group (p<0.0001). MADRS remitter rates (total score ≤12) at Week 8 were 28.93% (PBO) and 52.56% (DLX); p<0.0001. Time to sustained MADRS remission was considerably shorter for duloxetine than for placebo (p-value for the log rank test <0.0001).

For the 3 BPI-SF pain categories worst pain (p=0.0048), least pain (p=0.0054), and current pain ('right now'; p=0.0264), duloxetine treatment led to significant improvements compared with placebo (treatment-by-time interaction by MMRM). Duloxetine also reduced the interference of pain with daily activities (average score of the item-9 sub-scores of the BPI-SF analysed by ANCOVA): adjusted mean changes from baseline at Week 8 were −1.61 (PBO) and −2.76 (DLX) with a p-value of <0.0001 for the treatment difference.

Both for the somatic average score (p=0.0011) and the general symptomatic index of the SCL-90-R (p=0.0008) substantially better effects were achieved with duloxetine than with placebo after the 8-week treatment. Using the CGI-global improvement tool, the investigators considered the patients' overall condition at Week 8 as improved ('very much/much improved') in 42.14% (PBO) and 62.58% (DLX) of the patients (p=0.0018). Based on the PGI, 31.41% (PBO) and 51.28% (DLX) of the patients thought their condition had improved at Week 8 (p=0.0033).

In the treated set, the percentage of patients prematurely withdrawn for whatever reason (PBO: 22.4%, DLX: 25.3%) was similar in both groups (p=0.5206). Also, the frequency of discontinuations due to AEs (PBO: 5.5%, DLX: 10.5%) had a p-value greater than 0.05 (p=0.0939). Lack of efficacy caused 8.5% (PBO) and 1.9% (DLX) of the patients to discontinue the study prematurely.

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Safety results:

Mean total exposure was similar in both groups with 61.7 days for placebo and 59.9 days for duloxetine. During the treatment phase (i.e. escalation plus main phase), AEs were more frequent in the duloxetine group (55.6% of the patients) than in the placebo group (45.5%). The most commonly reported AE system organ classes (incidence >10% in either treatment group) were gastrointestinal disorders (PBO: 18.8%, DLX: 37.0%), nervous system disorders (PBO: 12.7%, DLX: 15.4%), infections and infestations (PBO: 10.9%, DLX: 11.7%), psychiatric disorders (PBO: 6.7%, DLX: 13.0%), skin and subcutaneous tissue disorders (PBO: 4.8%, DLX: 14.2%), and general disorders and administration site conditions (PBO: 4.2%, DLX: 11.7%). On preferred term level, the most frequent AEs (incidence >5% in either group) were nausea (PBO: 7.9%, DLX: 24.7%), hyperhidrosis (PBO: 2.4%, DLX: 11.7%), dry mouth (PBO: 3.6%, DLX: 10.5%), headache (PBO: 9.1%, DLX: 7.4%), nasopharyngitis (PBO: 5.5%, DLX: 6.2%), fatigue (PBO: 1.8%, DLX: 8.0%), dizziness (PBO: 3.6%, DLX: 5.6%), and constipation (PBO: 1.2%, DLX: 5.6%), a pattern consistent with the known safety profile of duloxetine.

Severe AEs affected 2.4% of placebo patients and 6.8% of duloxetine patients, all of which recovered from the events. The frequencies of drug-related AEs during treatment were 23.6% for placebo and 40.7% for duloxetine. The most common drug-related events (and more common with duloxetine than with placebo) were nausea (PBO: 6.1%, DLX: 21.6%), hyperhidrosis (PBO: 1.8%, DLX: 10.5%), dry mouth (PBO: 3.0%, DLX: 9.9%), and fatigue (PBO: 1.2%, DLX: 6.8%). During treatment, 5.5% of the placebo patients and 10.5% of the duloxetine patients had AEs that caused the patients to prematurely discontinue their treatment.

Serious AEs were experienced by 3 patients on duloxetine treatment (intentional self-injury; worsening of depression; road traffic accident with intracranial injury, haemopneumothorax, lumbar vertebral fracture, rib fracture, scapula fracture). None of the serious events was assessed as drug-related by the investigator; all patients recovered.

Pathologic liver function tests were pre-defined as significant AEs. In total, 3 patients in the treated set had such significant events (2 on placebo, 1 on duloxetine). The latter patient had a transient increase in serum creatine kinase concentration due to a crush syndrome. Other significant AEs occurred in 5.5% (PBO) and 8.6% (DLX) of the patients on treatment (escalation and main phase) and in 1 patient (0.8%) while taking 30 mg duloxetine (tapering phase).

In the tapering phase, 7.4% (PBO) and 9.5% (DLX) of the patients had AEs. Dizziness (PBO: 0.7%, DLX: 3.2%), vertigo (PBO: 0%, DLX: 2.4%), headache (PBO: 1.5%, DLX: 0.8%), and nausea (PBO: 1.5%, DLX: 0.8%) were the most

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Safety results: (continued)	common events. The analysis of laboratory parameters did not reveal clinically relevant changes or differences between the treatment groups. Only minimal changes of weight or blood pressure were observed during the study. Small mean increases of pulse rate (2-3 bpm) were noted in the duloxetine group. One placebo patient but 6 duloxetine patients had increases of pulse rate >100 bpm accompanied by an increase from baseline of ≥10 bpm.
Conclusions:	In this trial, 60 mg duloxetine given once daily for 7 weeks (following a 1-week escalation phase with 30 mg duloxetine) exhibited robust efficacy compared with placebo on painful physical and core depressive symptoms in patients with major depressive disorder. Efficacy was demonstrated by the reduction of the BPI-SF average pain score as the primary variable, the MADRS total score and a range of further secondary endpoints. Duloxetine treatment was well tolerated.