Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

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Title of trial:	A 12 weeks open label two parallel groups study to assess the efficacy of orally administered duloxetine 60 mg and 120 mg per day on treatment outcomes in patients with diabetic peripheral neuropathic pain with and without co-morbid major depressive disorder
Principal Investigator	[redacted]
Trial sites:	Multicentre study, 24 sites in Germany
Publication (reference):	Data of this study have not been published
Clinical phase:	IV
Objectives:	The general aim of this study was to evaluate whether 60 to 120 mg/day of duloxetine hydrochloride (duloxetine) led to a clinically relevant improvement as measured by the change in the Brief Pain Inventory 24 h average interference score (BPI-IS) from baseline to 12 weeks in diabetic peripheral neuropathic pain (DPNP) patients with and without co-morbid major depressive disorder (MDD). The efficacy of duloxetine was further evaluated based on endpoints for pain, depression, quality of life/functionality, and diabetes in DPNP patients both with and without MDD.
Methodology:	Open label, non-randomized trial with two parallel groups

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No. of subjects:	
planned:	entered: 166
actual:	enrolled: 133 entered: 108 Patients without MDD (MDD−): entered: 78 treated: 78 analysed (for efficacy endpoints): 74 Patients with major depressive disorder (MDD+): entered: 30 treated: 30 analysed (for efficacy endpoints): 30
Diagnosis and main criteria for inclusion:	Male or female patients ≥18 years of age that met the International Conference of Diseases (ICD-10) criteria for DPNP, had a score of ≥4 on the Brief Pain Inventory (BPI) 24 h average pain severity score, did not have an International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) diagnosis of MDD, and had an Hamilton Rating Scale for Depression (HAMD-17) score of <16 at screening and baseline were eligible for the MDD− arm of the study. For the MDD+ portion of the trial, patients also needed to meet the ICD-10 criteria for DPNP and have a score ≥4 on the BPI 24 h average pain severity score. They additionally needed to have an ICD-10 diagnosis of MDD and an HAMD-17 score ≥16 at screening and baseline.

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Test product:	Duloxetine hydrochloride capsules (duloxetine)
dose:	Treatment phase I: 30 mg/day duloxetine for 1 week followed by 60 mg/day duloxetine for 5 weeks. Treatment phase II: Responders[1] received 60 mg/day duloxetine for 6 weeks. Non-responders received 90 to 120 mg/day duloxetine for 6 weeks[2]. Tapering period: Responders received 30 mg/day duloxetine for 2 weeks. Non-responders received 60 mg/day duloxetine for 1 week followed by 30 mg/day duloxetine for 1 week. [1]Responders were patients with at least a 30% reduction in the BPI 24 h average pain item between Visits 2 and 5. Patients in the responder group could have been up-titrated to the non-responder group by the discretion of the investigator if they experienced worsening of symptoms. [2]Patients receiving 120 mg/day duloxetine could have received a dose reduction to 90 mg/day if tolerability concerns existed.
mode of admin.:	Oral
batch no.:	60 mg capsules A513719, 30 mg capsules A508387
Reference therapy:	Not applicable
Duration of treatment:	The duration of the treatment period was 12 weeks; this included a 1-week up-titration period, after which a minimum maintenance dose was taken for 11 weeks. After the 12-week treatment period, there was a 2-week taper phase.

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Criteria for evaluation:

Efficacy / clinical pharmacology:

The primary endpoint was the change in the BPI 24 h average interference score (BPI-IS) from baseline to 12 weeks of treatment with 60 to120 mg/day duloxetine.

Pain

Secondary endpoints used to evaluate the effect of 60 to 120 mg/day duloxetine on pain in patients with DPNP were the changes in individual BPI severity scores from baseline to 2, 6, and 12 weeks, the percentage of patients with a reduction in the BPI severity score for average pain over the last 24 h at 2, 6, and 12 weeks, the change in the Patient Global Impression of Improvement scale for pain (PGI-I) after 2, 6, and 12 weeks, and the change in Clinical Global Impression-Severity Scale (CGI-S) for pain after 2, 6, and 12 weeks.

Depression

Secondary endpoints to evaluate the effect of 60 to 120 mg/day duloxetine on depression in patients with DPNP included the change in the Beck Depression Inventory II (BDI-II) total score from baseline to 2, 6, and 12 weeks, the change in the 17-item Hamilton Rating Scale for Depression (HAMD-17) total score from baseline to 2, 6, and 12 weeks, and the change in the Hospital Anxiety and Depression Scale (HADS) depression and anxiety total scores from baseline to 2, 6, and 12 weeks.

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Efficacy / clinical pharmacology: (continued)	**Functionality and quality of life** In addition, secondary endpoints to evaluate 60 to 120 mg/day of duloxetine on functionality and quality of life in patients with DPNP included the change in the BPI-IS after 6 weeks, the change in each individual interference item on the BPI, the change in the West Haven-Yale Multidimensional Pain Inventory (MPI) from baseline to 6 and 12 weeks, and the changes in the mental and physical health components of the 12-item Short Form health survey (SF-12) from baseline to 6 and 12 weeks. **Diabetes** Secondary diabetic endpoints for the evaluation of duloxetine in patients with DPNP included changes in fasting blood glucose (FBG) and glycosylated haemoglobin A_{1c} (HbA_{1c}) from baseline to 12 weeks.
Safety:	Suicidal risk as analysed by changes in BDI-II item 9 and HAMD-17 item 3, treatment discontinuation rates, adverse events (AEs), physical examination, and changes in vital signs and clinical laboratory tests were used to evaluate safety.
Statistical methods:	The primary efficacy analysis on the BPI-IS was performed separately for the two groups (MDD− and MDD+) in a mixed model repeated measures (MMRM) analysis including data from all visits up to week 12. The model included terms for group, visit, group-visit interaction, investigator, baseline value, and baseline-visit interaction. An unstructured covariance matrix was used, and only in the case of non-convergence was a more restrictive covariance matrix to be used. Least square means for the change as well as for the absolute values were provided at baseline and for each post-baseline visit together with the respective standard errors and two-sided 95% confidence intervals (CIs). Duloxetine was to be considered effective in reducing the interference of pain on daily activities if the 95% CI for the mean change to week 12 was below −1.35.

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SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results

Although it was initially planned to have equal numbers of MDD− and MDD+ patients in this study, it was impossible to obtain the number planned for the MDD+ group within a reasonable time. Thus, per Protocol Amendment 2, the decision was made to stop further recruitment into the study. At the time of the decision to stop recruitment, study patients who were still under study treatment were to continue according to the study protocol until completion or until early discontinuation for reasons other than the study being stopped.

Despite the low number of MDD+ patients that took part in the study, both the MDD− and MDD+ groups were well balanced in terms of demographics and baseline characteristics.

Primary endpoint

Overall, 96.3% of all treated patients were included in the full analysis set (FAS), which was analysed for efficacy. The primary outcome measure for this study was the mean change in the BPI-IS from baseline to 12 weeks of duloxetine treatment. According to the change in this score, the overall interference from pain decreased significantly for patients both with and without depression from baseline to 12 weeks (MMRM analysis: MDD− patients −1.64, [95% CI from −2.05 to −1.23], MDD+ patients −1.78, [95% CI from −2.42 to −1.13]). The 2-sided 95% CI for the change from baseline, however, was found to include −1.35. It was noted that duloxetine was less effective at reducing the interference of pain on everyday functionality than it had been in previous studies.

Secondary endpoints

As this is a summary report, not all secondary endpoints are discussed in Section 11.4.1.2 of the Report; full analyses, however, can be found in Section 15.2.

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Efficacy / clinical pharmacology results: (continued)

Pain endpoints

Average pain, which was measured by the change in the BPI 24 h average pain severity score from baseline to 12 weeks, also decreased significantly over the course of the study regardless of depression status (MMRM analysis: MDD− patients −2.43 [95% CI from −2.92 to −1.93], MDD+ patients −2.16 [95% CI from −2.95 to −1.38]). Overall, a little more than half of patients (56.7%) were reported with a reduction ≥30% and approximately two-fifths (39.4%) of patients were reported with a reduction of ≥50% in the BPI 24 h average pain score after 12 weeks of taking duloxetine; the percentages of patients with a reduction in this pain score were similar between the MDD− and MDD+ groups. Furthermore, the individual BPI severity scores for 'worst pain', 'least pain', and 'pain right now' all improved (decreased) from baseline to 12 weeks.

Depression endpoints

Measurements of depression with the BDI-II, HAMD-17, and HADS scales indicated that overall depression levels decreased over the course of this 12 week study with duloxetine. The MDD+ group was reported with an approximately 5-fold larger improvement in depression from baseline to 12 weeks as measured by the BDI-II score (unadjusted mean BDI-II change [±SD]: MDD− patients −1.6 [±6.02], MDD+ patients −7.8 [±7.25]). MDD+ patients were also reported with an approximately 12-fold larger improvement in the mean HAMD-17 score as compared with MDD− patients (unadjusted mean HAMD-17 change [±SD]: MDD− patients −0.8 [±3.30], MDD+ patients −9.7 [±5.50]). Finally, on average both the HADS anxiety and depression total scores improved during the 12-week study for both MDD+ and MDD− patients. The MDD+ group was reported with an approximately 5.3-fold larger improvement in depression as compared to the MDD− group as measured by the HADS depression total score (unadjusted mean HADS depression total score change [±SD]: MDD− patients −0.7 [±3.07], MDD+ patients −3.7 [±3.92]). In terms of the HADS anxiety total score, the MDD+ group was reported with an approximately 3.3-fold larger improvement (unadjusted mean HADS anxiety total score change [±SD]: MDD− patients −1.0 [±3.03], MDD+ patients −3.3 [±4.08]).

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Efficacy / clinical pharmacology results: (continued)

Quality of life and functionality endpoints

Overall, both MDD− and MDD+ patients reported a similar decrease in the amount of interference from pain as measured by the BPI-IS after 6 weeks of treatment with duloxetine (MMRM analysis: MDD− patients −1.28 [95% CI from −1.69 to −0.88], MDD+ patients −1.55 [95% CI from −2.19 to −0.90]). Finally, the BPI individual severity scores for the interference of pain with 'general activity', 'mood', 'walking ability', 'normal work', 'relationships', 'sleep', and 'enjoyment of life' all improved (decreased) from baseline to 12 weeks, with the scores from the MMRM analysis for 'general activity' and 'walking ability' showing the most improvement for both groups. Before statistical adjustment of the scores in the MMRM analysis, however, the MDD− patients were reported with the most improvement in interference scores for 'general activity' and 'walking ability', and the MDD+ patients were reported with the most improvement in the interference scores for 'mood' and 'general activity'.

Diabetic endpoints

Both MDD− and MDD+ patients exhibited a small, non-significant increase in FBG from baseline to week 12, while HbA_{1c} remained stable over the same time period. For MDD− patients, the least squares mean change from baseline to week 12 in FBG was 14.9 mg/dL (95% CI from −12.0 to 41.8; p=0.243); a similar value of 13.0 mg/dL (CI from −37.7 to 63.7; p=0.575) was observed for MDD+ patients.

Analyses on the FAS without patients [redacted]

During review of this CTR, it was discovered that 3 patients ([redacted]) had been included in the FAS although they were given incorrect dosages of study drug. Patient [redacted] received 90 mg/day duloxetine before Visit 5 from the third treatment week on, and Patients [redacted] and [redacted] received 120 mg/day duloxetine before Visit 5 from the third treatment week on. Thus, an additional efficacy analysis was carried out without these patients in the FAS. In general, all endpoints for the FAS without patients [redacted] were similar to the corresponding endpoints for the FAS including these patients.

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Safety results:

The overall mean exposure time to duloxetine was 10.03 weeks (±4.39 weeks), and a majority of patients (86 patients, 79.6%) were exposed to the study drug for longer than 6 weeks. Although 30.6% had discontinued treatment before the end of the study, more than half of all treated patients (53.7%) continued taking commercial duloxetine after the study was over.

Overall, a total of 64 patients (59.3%) were reported with AEs during this study. Patients were most frequently reported with AEs in the system organ classes (SOCs) gastrointestinal disorders (25.0%), nervous system disorders (14.8%), skin and subcutaneous disorders (14.8%), and musculoskeletal and connective tissue disorders (12.0%). On a PT level, patients were most frequently reported with hyperhidrosis (13.0%), nausea (13.0%), diarrhoea (6.5%), fatigue (6.5%), constipation (5.6%), and back pain (4.6%). Small differences between the MDD− and MDD+ groups were seen for the occurrence of some AEs; however, in general AE occurrence was well matched between the two groups.

The majority of AEs were reported to be of mild or moderate intensity; however, a total of 7 patients (6.5%) were reported with AEs of severe intensity. No patients were found to be at suicidal risk; no patients had a score greater than 2 on BDI-II item 9 during the course of this study. Slightly less than half (45 patients, 41.7%) of patients were reported with investigator-defined drug-related AEs. Furthermore, a total of 23 patients (21.3%) were reported with AEs that led to premature drug discontinuation.

A total of 6 patients (5.6%) were reported with SAEs. Patients were most commonly reported with SAEs in the SOCs cardiac disorders and nervous system disorders. There was 1 fatal case in the MDD− group during the course of this study; the fatal SAE (worsening of cardiac failure) was not considered by the investigator to be related to the study drug. Other significant events as defined by ICH E3 were reported for a total of 26 patients (24.1%).

Although a few patients were reported with possibly clinically significant abnormalities in laboratory values, no laboratory or vital sign findings were determined to be clinically relevant by the investigator. Overall, treatment with duloxetine was considered safe and no major safety issues were identified.

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Conclusions: Although duloxetine was not as effective at reducing the overall interference from pain as measured by the mean change in the BPI-IS from baseline to 12 weeks as it had been in previous studies, its use nevertheless led to improvements in pain, depression, and quality of life and functionality endpoints for both MDD− and MDD+ patients with DPNP. In general, the improvement in pain-related endpoints was similar in the 2 groups. Patients with MDD, however, were reported with much larger improvements in depression-related endpoints. Duloxetine was considered safe and was well tolerated by both MDD− and MDD+ patients with DPNP. No major safety issues with duloxetine were identified during this study.