Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Title of trial:	An 8-week, randomised, double-blind, two parallel group study to assess clinical response to duloxetine 60 mg and 120 mg per day in patients hospitalised for severe depression
Coordinating Investigator:	[redacted]
Trial sites:	Multi-centre study, 34 sites in 4 countries.
Publication (reference):	Data of this study have not been published
Clinical phase:	IV
Objectives:	To show superiority for 120 mg daily duloxetine over 60 mg daily duloxetine in patients hospitalised for severe major depression after 4 weeks of treatment. The study also evaluated a rescue option for non-responding patients and the safety of duloxetine. Patients discontinuing treatment at Visit 3 or later, were to undergo treatment switch or enter a duloxetine taper-down treatment phase.
Methodology:	Randomised, double-blind, 2 parallel group (60 and 120 mg daily duloxetine administered orally), multi-centre trial with 8 weeks of treatment (with a dose escalation option for non-responding patients). At Week 4, patients classified by the investigator as non-responders were up-titrated to receive 120 mg duloxetine.
No. of subjects:	
planned:	entered: 324
actual:	enrolled: 392 entered: 339 Duloxetine 60 mg daily: entered: 167 treated: 167 analysed (for primary endpoint): 166 Duloxetine 120 mg daily: entered: 172 treated: 171 analysed (for primary endpoint): 170

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Diagnosis and main criteria for inclusion:	Male or female patients of ≥18 years of age that met the criteria for severe major depressive disorder, without psychotic features. At both screening and baseline, total Montgomery-Åsperg depression rating scale (MADRS) score ≥30, 6-item Hamilton Depression scale (HAMD-6) score ≥12 and Clinical Global Impression of Severity (CGI-S) score ≥4. Patients willing and able to comply with the requirement for hospitalisation (at least up to Visit 4) and with all scheduled visits, tests and procedures required by the protocol.
Test product:	Duloxetine capsules
dose:	60 mg capsules for the treatment phase given as a daily dose of 60 or 120 mg
mode of admin.:	oral
batch no.:	B061002054
Test product:	Duloxetine capsules
dose:	30 mg capsules for the taper-down phase given as a daily dose of 30 or 60 mg
mode of admin.:	oral
batch no.:	B061002056
Reference therapy:	Matching placebo capsules
dose:	0 mg
mode of admin.:	oral
batch no.:	B061002055, B061002080
Duration of treatment:	An 8-week double-blind treatment phase, plus an optional 2-week double-blind taper-down phase

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Criteria for evaluation:

Efficacy / clinical pharmacology:

Primary efficacy criteria:

- Change in MADRS total score from baseline to week 4

Secondary efficacy criteria:

- Change in HAMD-6 total score
- Change in MADRS total score from baseline (at the other visits)
- Evaluation of the treatment rescue option
- The proportion of patients responding to treatment
- The proportion of patients acheiving remission
- Change in CGI-Severity of Illness score
- Change in CGI-Improvement score
- Change in Patient Global Impressions of Improvement (PGI-I) score
- The change in Hamilton Scale of Anxiety (HAMA) score
- Reason for Living (RFL) questionnaire
- Utilisation of allowed hypnotic and anxiolytic comedications

Safety:

Treatment-emergent adverse events (AEs), change in vital signs and weight, change in safety laboratory assessments, withdrawals due to AEs.

Statistical methods:

At Week 4, the primary efficacy outcome, was assessed by covariance analysis with stratification factors and baseline MADRS score as covariates. Least square means were calculated to compare treatment means to zero and with each other. Potential prognostic factors were investigated in an exploratory model, with baseline parameters of demographic characteristics, disease history and baseline MADRS score.

At Week 4, other continuous endpoints were assessed by covariance analysis with stratification factors and baseline MADRS score as covariates. Responder rate was compared between groups using a logistic regression model with stratification factors and baseline MADRS total or HAMD-6 score as covariates. In order to evaluate the rescue option from Week 4 to Week 8, all endpoints were described according to 4 patient groups: 60 mg responders, 60 mg non-responders, 120 mg responders, and 120 mg non-responders. Within-group comparisons were performed for 60 mg responders and 60 mg non-responders using the Sign Rank test.

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SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

Overall 392 patients were enrolled into the study, of whom 339 were randomised to treatment. A total of 338 patients were treated in either the duloxetine 60 mg (167 patients) or duloxetine 120 mg (171 patients) groups. A total of 53 patients discontinued the trial medication prematurely, comprising 24 patients (14.4%) in the duloxetine 60 mg group and 29 patients (17.0%) in the duloxetine 120 mg group. The most common reasons for premature study discontinuation were the occurrence of AEs (20 patients; 5.9%), comprising other AEs (12 patients; 3.6%) and unexpected worsening of the study disease (8 patients; 2.4%). In the duloxetine 60 mg group 11 patients discontinued study participation due to an AE, all discontinuing patients were classified as non-responders to the study treatment at Week 4. In the duloxetine 120 mg group 9 patients discontinued study participation due to an AE, with 1 patient being classified as a responder to the study treatment and 8 patients classified as non-responders.

Demographic characteristics were comparable for both dose groups: most patients were white (96.4% in the duloxetine 60 mg group and 95.3% in the duloxetine 120 mg group) and female (70.7% and 77.8%); the mean ages of the study groups were 45.7 years for duloxetine 60 mg and 43.9 years for duloxetine 120 mg treated patients; 43.7% of patients in the duloxetine 60 mg group and 42.7% in the duloxetine 120 mg group were considered treatment naive for major depressive disorder. Overall, 87.0% of patients had experienced at least one previous major depressive disorder episode. The concomitant diagnoses most frequently seen were insomnia (47.3%) and anxiety (43.2%).

The primary endpoint of the study was the change in MADRS score between baseline and Week 4. There was no difference in the degree to which MADRS score changed from baseline to Week 4 when comparing patients treated with duloxetine 60 mg or 120 mg (p = 0.88), as summarised below.

	Duloxetine 60 mg	Duloxetine 120 mg
MADRS score, mean (SD)		
Baseline	36.1 (4.0)	36.0 (4.6)
Week 4	16.0 (11.1)	16.2 (10.8)
Change in MADRS score, mean (SD)	-20.1 (10.6)	-19.9 (10.0)

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The results obtained for a number of secondary endpoints supported a comparable treatment effect for the 2 duloxetine doses. After 8 weeks of treatment: duloxetine 60 mg resulted in a mean change in MADRS total score of -25.2 (SD = 10.8) and duloxetine 120 mg in a change of -24.9 (SD = 10.9); both duloxetine doses resulted in a mean change in RFL questionnaire total score of 0.6 (SD = 0.9). After 4 weeks of treatment: duloxetine 60 mg resulted in a mean change in HAMD-6 score of -8.0 (SD = 4.8) and duloxetine 120 mg in a change of -8.1 (SD = 4.7); duloxetine 60 mg resulted in a mean change in HAMA total score of -13.0 (SD = 9.0) and duloxetine 120 mg in a change of -13.6 (SD = 9.0). Symptom improvement was also seen for both dose groups in terms of: mean CGI-S score (duloxetine 60 mg resulted in a reduction from 5.0 to 3.0 and duloxetine 120 mg from 5.1 to 3.1); mean CGI-I score (duloxetine 60 mg resulted in a reduction from 3.1 to 2.3 and duloxetine 120 mg from 3.2 to 2.1); and mean PGI-I score (duloxetine 60 mg resulted in a reduction from 3.0 to 2.3 and duloxetine 120 mg from 3.1 to 2.2).

The proportion of patients classified as MADRS responders was comparable for the duloxetine dose groups at 4 weeks (59.0% for the duloxetine 60 mg group and 64.1% for the 120 mg group, $p = 0.32$). Similar findings were seen after 4 weeks of treatment for HAMD-6 responders (55.4% versus 58.2%, $p = 0.57$).

MDD remission was defined as a total MADRS score of ≤ 12 after 8 weeks of treatment. MDD remission was achieved by 68.7% of patients in the duloxetine 60 mg group and 65.9% of patients in the duloxetine 120 mg dose group. In the duloxetine 60 mg dose group 88.5% of patients classified as treatment responders (at Week 4) and 41.4% of non-responding patients achieved remission. In the duloxetine 120 mg dose group 88.7% of responding patients and 28.1% of non-responding patients were classified as achieving remission. Dose increase for non-responding patients receiving duloxetine 60 mg was associated with a remission for about 40% of patients. However, almost 30% of non-responding patients in the duloxetine 120 mg dose group also experienced remission.

The use of medications to alleviate anxiety and sleep disturbances decreased over the course of the study for both duloxetine dose groups, with a comparable incidence of use being seen for both groups at each study visit.

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	Dose escalation in patients not responding to duloxetine 60 mg therapy after 4 weeks of treatment was associated with some evidence of clinical improvement. Prior non-responders in the duloxetine 60 mg group showed a 65.7% MADRS response rate by Week 8. However prior non-responders in the duloxetine 120 mg dose group, though not dose-escalated, showed a smaller clinical improvement in terms of a 54.7% MADRS response rate by Week 8.
Safety results:	The 338 patients who entered the treatment phase of the study received at least one dose of duloxetine, achieving a mean duration of exposure of 55.1 days. During active treatment, 97 patients (58.1%) in the duloxetine 60 mg group and 89 patients (52.0%) in the duloxetine 120 mg dose group reported at least one AE. For both dose groups a higher incidence of AEs was apparent during the first 4 weeks of study treatment (47.9% vs. 21.1% during Weeks 5 to 8 for responding patients receiving 60 mg duloxetine; 50.0% vs. 21.7% during Weeks 5 to 8 for responding patients receiving 120 mg duloxetine); few patients experienced AEs during duloxetine taper-down (2 responding patients in the 6 mg dose group and 1 responding patient in the 120 mg group) or post-study (2 responding patients in each dose group). The most frequent AEs in patients randomised to 60 mg duloxetine were classified as gastrointestinal (at incidences of 32.3% in responding patients and 31.0% in non-responding patients during Weeks 1 to 4), nervous system (24.0% and 19.7%) and skin and subcutaneous (12.5% and 4.2%) disorders. The most frequent AEs in patients randomised to 60 mg duloxetine were nausea (at incidences of 18.8% in responding patients and 19.7% in non-responding patients during Weeks 1 to 4) and headache (13.5% and 14.1%). The most frequent AEs in patients randomised to 120 mg duloxetine were classified as gastrointestinal (at incidences of 29.2% in responding patients and 18.5% in non-responding patients during Weeks 1 to 4) and nervous system (18.9% and 16.9%) disorders. The most frequent AEs in patients randomised to 120 mg duloxetine were nausea (15.1% in responding patients and 6.2% in non-responding patients during Weeks 1 to 4) and headache (8.5% and 12.3%); in addition 9.2% of non-responding patients experienced constipation during Weeks 1 to 4. There was no indication that the higher treatment dose was associated with an increased incidence of AEs.

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The majority of AEs had a worst intensity of either mild (31.1% for the duloxetine 60 mg group and 24.6% for the duloxetine 120 mg group) or moderate (21.6% and 22.2%). AEs of severe intensity were reported with similar frequencies in the duloxetine dose groups (5.4% and 5.3%). During active treatment, 65 patients (38.9%) in the duloxetine 60 mg group and 58 patients (33.9%) in the duloxetine 120 mg group experienced AEs considered drug-related. The most frequent AEs assessed as drug-related were nausea (18.0% for duloxetine 60 mg and 10.5% for duloxetine 120 mg), headache (4.8% and 7.6%) and dry mouth (4.8% and 6.4%).

No patients died during the trial. During the active treatment phases, 7 patients (4.2%) in the duloxetine 60 mg group experienced SAEs of: suicide attempt (4 patients), suicidal ideation (3 patients), and self-injurious behaviour, irritability and back pain (all 1 patient). Six patients (3.5%) in the duloxetine 120 mg group experienced SAEs of: anxiety and depression (both 2 patients), and brain neoplasm and serotonin syndrome (both 1 patient). SAEs considered drug-related occurred in individual patients and comprised: suicidal ideation and irritability (60 mg dosing), suicide attempt (120 mg dosing following dose escalation in a patient randomised to duloxetine 60 mg) and serotonin syndrome (120 mg dosing).

Significant AEs were specified by the trial protocol as events indicative of hepatic dysfunction. Significant AEs were reported for 4 patients (2.4%) during treatment with duloxetine 60 mg comprising: increased ALT and increased blood bilirubin (both 2 patients) and increased AST and increased GGT (both 1 patient). Significant AEs were experienced by 3 patients (1.8%) during treatment with duloxetine 120 mg comprising: increased blood bilirubin (2 patients) and increased ALT (1 patient).

Other significant AEs were observed in 6 patients (3.6%) during treatment with duloxetine 60 mg and comprised: hypothyroidism, depression, major depression, psychotic disorder, schizoaffective disorder, headache, and nausea (all 1 patient). Other significant AE were experienced by 5 patients (2.9%) during treatment with duloxetine 120 mg and comprised: suicidal ideation, dizziness, sedation, upper abdominal pain, drug eruption, renal failure, and urinary retention (all 1 patient).

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	Eleven patients (6.6%) in the duloxetine 60 mg group reported an AE leading to premature discontinuation of trial drug intake comprising: suicide attempt (3 patients); suicidal ideation (2 patients); hypothyroidism, depression, major depression, psychotic disorder, schizoaffective disorder, self-injurious behaviour, headache, nausea and irritability (all 1 patient). Nine patients (5.3%) in the duloxetine 120 mg group experienced AEs that led to treatment discontinuation comprising: depression (2 patients); brain neoplasm, suicidal ideation, dizziness, sedation, serotonin syndrome, upper abdominal pain, drug eruption, renal failure and urinary retention (all 1 patient). Changes in laboratory safety assessment parameters were seen for a small proportion of patients in both duloxetine dose groups. Potentially clinically significant changes were rare, occurring in a maximum of 4% of patients (for an individual laboratory parameter) in the duloxetine 60 mg group and 2% of patients in the duloxetine 120 mg group. No relevant findings were seen in the analysis of vital signs (blood pressure and heart rate).
Conclusions:	Both duloxetine doses assessed in this study showed a high level of efficacy in patients who had been hospitalised for severe depression. In this patient population, treatment over 4 weeks with duloxetine was demonstrated as being safe and efficacious for both treatment regimens. Statistical analysis did not show a significant difference in efficacy between the two treatment arms. The lack of additional efficacy benefit for the higher dose was supported by the findings of the secondary efficacy endpoints of: HAMD-6 total score, change in MADRS total score over the duration of the trial, CGI-S score, CGI-I score PGI-I score, HAMA score, RFL questionnaire findings, response and remission rates, and the use of hypnotic, anxiolytic and rescue treatments. The proportion of patients classified as MADRS responders was comparable for the duloxetine dose groups at 4 weeks (59% for the duloxetine 60 mg group and 64% for the 120 mg group) and 8 weeks (64% and 82%, respectively). The safety profile for the duloxetine 60 mg and 120 mg doses were consistent with those reported; no safety concerns were associated with use of the duloxetine 120 mg dose.