Synopsis – Study 10990

Title of Study A double-blind, randomised, multi-centre, comparative study of escitalopram and duloxetine in outpatients with Major Depressive Disorder
Investigators 34 investigators in 9 countries *Signatory investigator* – Alan G Wade, MB, ChB, FRCA, CPS Research, Glasgow, United Kingdom
Study Centres 34 centres – 3 in Belgium, 4 in Canada, 6 in the Czech Republic, 5 in France, 7 in Germany, 2 in Italy, 3 in Spain, 3 in Sweden, and 1 in the United Kingdom
Publication Wade A, Gembert K, Florea I. A comparative study of the efficacy of acute and continuation treatment with escitalopram *versus* duloxetine in patients with major depressive disorder. *Curr Med Res Opin* 2007: 23; 1605-1614
Study Period *First patient first visit* – 23 September 2005 *Last patient last visit* – 12 September 2006
Objectives • *Primary objective*: – to compare the efficacy of escitalopram with that of duloxetine in outpatients with Major Depressive Disorder (MDD) after 24 weeks of treatment • *Secondary objectives*: – to compare the efficacy of escitalopram with that of duloxetine per visit over the 24-week study period in outpatients with MDD – to compare the tolerability and safety of escitalopram with that of duloxetine per visit over the 24-week study period in outpatients with MDD – to evaluate the discontinuation-emergent signs and symptoms during and after taper-down treatment with escitalopram or duloxetine after 24 weeks of treatment – to evaluate the impact of treatment with escitalopram or duloxetine on quality of life in patients with MDD – to evaluate the utilisation of resources in patients with MDD treated with escitalopram or duloxetine
Methodology • Multinational, multi-centre, randomised, double-blind, parallel-group, active-comparator, fixed-dose study of escitalopram *versus* duloxetine in patients with MDD. • The study consisted of the following periods: – 24-week Treatment Period – 24-week double-blind treatment period with either escitalopram 20 mg/day or duloxetine 60 mg/day. For the first 2 weeks, the escitalopram dose was 10 mg/day. – Taper Period – 2-week double-blind down-tapering period with escitalopram 10 mg/day or duloxetine 30 mg/day – Placebo Period – 1-week single-blind period with placebo – Safety Follow-up Period – 1-week safety follow-up period

Number of Patients Planned and Analysed

- 260 were planned for enrolment: 130 in each treatment group
- Patient disposition is tabulated below:

	Duloxetine 60mg/day		Escitalopram 20mg/day		Total	
	n	(%)	n	(%)	n	(%)
Patients randomised	151		144		295	
Patients treated (all-patients-treated set [APTS]):	151		143		294	
Patients completed	114	75.5	112	78.3	226	76.9
Patients withdrawn	37	24.5	31	21.7	68	23.1
Primary reason for withdrawal:						
Adverse event(s)	26	17.2	13	9.1	39	13.3
Lack of efficacy	2	1.3	7	4.9	9	3.1
Analysis sets:						
APTS	151		143		294	
Full-analysis set (FAS)	146		141		287	
Per-protocol set (PPS)	124		122		246	
All-patients-completed set (APCS)	114		112		226	

Diagnosis and Main Inclusion Criteria

Outpatients with a primary diagnosis of MDD according to DSM-IV-TR criteria, who:

- had a Montgomery and Åsberg Depression Rating Scale (MADRS) total score ≥26 and a Clinical Global Impression – Severity of Illness (CGI-S) score ≥4 at baseline
- were between 18 and 65 years of age (extremes included)

Investigational Product, Dose and Mode of Administration, Batch Number

Escitalopram – 20 mg/day; encapsulated tablets, orally; batch Nos. R135-05 (10 mg), R156-05 (10 mg), R136-05 (20 mg), and R155-05 (20 mg)

Duration of Treatment

24 weeks of double-blind treatment, 2 weeks of double-blind taper-down, and 1 week of single-blind placebo

Reference Therapy, Dose and Mode of Administration, Batch Number

Duloxetine – 60 mg/day; encapsulated capsules, orally; batch Nos. R125-05 (30 mg), R159-05 (30 mg), R126-05 (60 mg), and R160-05 (60 mg)

Placebo – encapsulated tablets, orally; batch Nos. R137-05 and R154-05

Criteria for Evaluation – Efficacy

- *Primary variable*:
  - change from baseline to Week 24 and to Week 8 in MADRS total score
- *Secondary variables*:
  - mean change from baseline to each visit in MADRS total score
  - mean change from baseline to each visit in $MADRS_6$ subscale score
  - mean change from baseline to each visit in Hamilton Rating Scale for Depression, 17-item ($HAM\text{-}D_{17}$) total score
  - mean change from baseline to each visit in Hamilton Rating Scale for Depression, 6-item ($HAM\text{-}D_6$) total score
  - mean change from baseline to each visit in Hamilton Rating Scale for Anxiety (HAM-A) total score
  - mean change from baseline to each visit in CGI-S score
  - Clinical Global Impression – Global Improvement (CGI-I) score at each visit
  - proportion of patients with a ≥50% reduction in MADRS total score (MADRS responders) at each visit
  - proportion of patients with a MADRS total score ≤12 (MADRS remitters) at each visit
  - mean change from baseline to Week 8 and to Week 24 in Sheehan Disability Scale (SDS) total score and subscores

Criteria for Evaluation – Efficacy (Continued)

– mean change from baseline to Weeks 4, 12 and 24 in Medical Outcomes Study (MOS) 36-item Short-form Health Survey (SF-36) individual indices

Criteria for Evaluation – Safety

Adverse events (AEs), clinical safety laboratory tests, vital signs, Discontinuation Emergent Signs and Symptoms (DESS)

Criteria for Evaluation – Pharmaco-economic Assessments

Health Economic Assessment (HEA) Questionnaire; reported elsewhere

Statistical Methods

- The following analysis sets were used:
  - *all-patients-randomised set* (APRS) – all randomised patients
  - *all-patients-treated set* (APTS) – all patients in the APRS who took at least one dose of double-blind investigational medicinal product (IMP)
  - *full-analysis set* (FAS) – all patients in the APTS who had at least one valid post-baseline assessment of the primary efficacy variable (MADRS total score)
  - *per-protocol set* (PPS) – all patients in the FAS who:
    - did not violate any relevant inclusion or exclusion criteria
    - received double-blind IMP up until the Week 4 visit
    - had at least one valid assessment of MADRS total score following 4 weeks of double-blind treatment
  - *all-patients-completed-set* (APCS) – all patients in the FAS who completed the first 24 weeks of double-blind treatment
- All efficacy analyses were conducted on the FAS (observed cases [OC] and last observation carried forward [LOCF]) unless otherwise specified. The primary efficacy analysis was repeated on the PPS to evaluate the robustness of the primary analysis results, as well as on the APTS to evaluate the effect of early withdrawals (before the first post-baseline efficacy assessment). The primary efficacy analysis was also repeated on the FAS with Centre FR003 excluded, due to a site audit finding. All safety analyses were conducted on the APTS, except for the DESS analysis, which was conducted on the APCS.
- *Primary efficacy analysis* – The change from baseline to Week 24 and to Week 8 in MADRS total score (LOCF) was analysed using analysis of covariance (ANCOVA), adjusting for centre and the baseline score. The analysis was a one-sided non-inferiority test of escitalopram *versus* duloxetine followed by a one-sided superiority test of escitalopram over duloxetine at the 5% level of significance. The hypotheses were analysed hierarchically in the following stepwise manner: i) non-inferiority at Week 24; ii) non-inferiority at Week 8; iii) superiority at Week 24; iv) superiority at Week 8. Each step was performed only if the preceding hypothesis was confirmed.
- *Secondary efficacy analyses* – The change from baseline to each visit in MADRS total score was analysed using a two-sided ANCOVA (LOCF, OC) and using a repeated measures method, adjusting for centre and the baseline score. The changes from baseline in $MADRS_6$, HAM-D_{17}, HAM-D_6, and HAM-A total scores, CGI-S score, SDS total score and subscale scores, and SF-36 subscale scores were analysed using two-sided ANCOVA adjusting for centre and baseline. The CGI-I score was analysed using a two-sided ANCOVA, adjusting for centre and the baseline CGI-S score. The proportion of patients who responded to treatment, based on the MADRS total score, and the proportion of patients who achieved remission, based on the MADRS total score, were analysed by visit using logistic regression and adjusting for centre and the baseline MADRS total score. For the subgroup of severely depressed patients (baseline MADRS total score ≥30), the change from baseline to each visit in MADRS total score, the proportion of patients who responded to treatment, and the proportion of patients who achieved remission were analysed as above.

Statistical Methods (Continued)

- *Safety analyses* – Logistic regression and Fisher's exact test were used to compare the incidence of adverse events and the incidence of withdrawals (by reason for withdrawal) between treatment groups. Kaplan-Meier plots were used for analyses of time to withdrawal, and point prevalence plots were constructed for adverse events with an incidence ≥5% during the 24-week Treatment Period. Clinical safety laboratory values and vital signs, and changes therein from screening to each assessment, were summarised using descriptive techniques. Values outside the normal range, as well as potentially clinically significant (PCS) values, were flagged and tabulated. DESS scores were analysed using the DESS score at Visit 9 (end of Week 24) as baseline. Change from baseline in DESS total score was analysed using 2-sided ANCOVA. The proportion of patients with a discontinuation syndrome (defined as an increase in DESS total score ≥4) was analysed using logistic regression.

Demography of Study Population

- The majority (96%) of the patients were Caucasian, the ratio of women to men was approximately 3:1, and the mean age was 43 years.
- At baseline, there were no statistically significant differences in height, weight, or body mass index between the treatment groups.
- At baseline, there were no statistically significant differences in efficacy scores between the treatment groups. The mean baseline MADRS total score was 32, indicating a population with moderate to severe depression.

Efficacy Results

- *Primary efficacy analysis*:
  - Escitalopram was non-inferior to duloxetine in reducing the MADRS total score from baseline to Week 24, and to Week 8 (FAS, LOCF, one-sided ANCOVA). In the superiority test, the null hypothesis of no treatment difference between escitalopram and duloxetine was not rejected at Week 24 (FAS, LOCF, one-sided ANCOVA).
  - When repeating the primary efficacy analysis on the APTS, escitalopram was superior to duloxetine in reducing the MADRS total score from baseline to Week 24, and to Week 8 (LOCF, one-sided ANCOVA).
  - When repeating the primary efficacy analysis on the PPS, or on the FAS with Centre FR003 excluded, escitalopram was non-inferior to duloxetine in reducing the MADRS total score from baseline to Week 24, and to Week 8. In the superiority test, the null hypothesis of no treatment difference between escitalopram and duloxetine was not rejected at Week 24 (LOCF, one-sided ANCOVA).
- *Secondary efficacy analyses*:
  - In the secondary efficacy analyses, escitalopram was generally numerically superior to duloxetine throughout the 24-week Treatment Period (LOCF and OC). Duloxetine was not statistically significantly superior to escitalopram at any time point in any secondary efficacy analysis.
  - In the secondary efficacy analysis of the MADRS, escitalopram was superior to duloxetine in reducing the MADRS total score from baseline. The difference was statistically significant from Week 1 to Week 16, with a treatment difference ranging from 1.2 points at Week 1 up to 2.4 points at Week 16 (LOCF, two-sided ANCOVA). In a repeated measures analysis of the MADRS total score, escitalopram was numerically, but not statistically significantly, superior to duloxetine throughout the 24-week Treatment Period.
  - In patients with a baseline MADRS total score ≥30, escitalopram was numerically superior to duloxetine throughout the 24-week Treatment Period in reducing the MADRS total score from baseline. The treatment difference was statistically significant at Week 1 (LOCF).
  - Escitalopram was statistically significantly superior to duloxetine in reducing the $MADRS_6$ total score from baseline to Week 16 (LOCF) and in reducing the $HAM\text{-}D_{17}$ total score from baseline to Weeks 1, 12, and 16 (LOCF).
  - Escitalopram was as efficacious as duloxetine in reducing anxiety symptoms assessed with the HAM-A, and statistically significantly superior to duloxetine in reducing the HAM-A total score from baseline to Week 1 (LOCF).
  - Escitalopram was as efficacious as duloxetine in reducing the CGI-S score and statistically significantly superior to duloxetine in improving the CGI-I score from baseline to Weeks 2, 8, and 16 (LOCF).

Efficacy Results (Continued)

- Escitalopram was superior to duloxetine in alleviating patient-reported life impairment. Escitalopram statistically significantly improved the SDS total score more at Week 8 and at Week 24; and the SDS social and family life subscale scores at Week 8, as well as the SDS work subscale score at Week 24 (LOCF). Furthermore, escitalopram was as efficacious as duloxetine in improving quality of life assessed with the SF-36 subscale scores at Weeks 4, 12, and 24. For SF-36 item 2 (health transition), the treatment difference in favour of escitalopram was statistically significant at Week 12 (LOCF).
- The overall response rate, defined as a ≥50% reduction from baseline in MADRS total score, was numerically better for escitalopram than for duloxetine throughout the 24-week Treatment Period, and statistically significant at Weeks 8, 12, and 16 (a difference of 10 to 11 precentage points, LOCF).
- The overall remission rate, defined as a total MADRS score ≤12, was better for escitalopram than for duloxetine from Week 2 and throughout the 24-week Treatment Period, but the treatment difference was not statistically significant.

Safety Results

- The adverse event incidence for the study is summarised below:

	Duloxetine 60mg/day		Escitalopram 20mg/day	
	n	(%)	n	(%)
Entire Study (APTS)				
Patients who died	1		0	
Patients with serious AEs (SAEs)	6	(4.0)	2	(1.4)
Patients with TEAEs	119	(78.8)	118	(82.5)
Total number of TEAEs	619		594	
24-week Treatment Period (APTS)				
Patients who died	1		0	
Patients with serious AEs (SAEs)	6	(4.0)	2	(1.4)
Patients with TEAEs	113	(74.8)	111	(77.6)
Total number of TEAEs	530		477	
Taper Period (APCS)				
Patients with TEAEs	22	(19.3)	22	(19.6)
Placebo Period (APCS)				
Patients with TEAEs	22	(19.3)	26	(23.2)

n = number of patients; % = percentage of patients within treatment group

- One patient (in the DUL group) died during the study. The patient stopped taking IMP after 3 days and committed suicide by hanging himself on Day 8. The investigator considered the event *possibly related* to IMP.
- In the 24-week Treatment Period, 9 SAEs were reported in 8 patients: 6 patients in the DUL group (including the patient who died) and 2 patients in the ESC group. The investigators considered 2 of the SAEs (worsening of angina pectoris, and epistaxis) in the DUL group *possibly related* to IMP. There were no trends in the types or incidences of SAEs between or within the treatment groups.
- In the 24-week Treatment Period, statistically significantly more patients in the DUL group withdrew due to adverse events than did patients in the ESC group (17% *versus* 9%). The adverse event leading to withdrawal with the highest incidence in both treatment groups was nausea. In the DUL group, agitation and insomnia led to withdrawal in 6 and 4 patients, respectively. In the ESC group, no adverse event other than nausea led to withdrawal in more than 2 patients.

Safety Results (Continued)

- In the 24-week Treatment Period, 75% of the patients in the DUL group and 78% of the patients in the ESC group had TEAEs. In the DUL group, the TEAEs with an incidence ≥5% were: nausea (32%), headache (17%), dizziness (16%), dry mouth (13%), insomnia (13%), fatigue (11%), constipation (9%), nasopharyngitis (7%), diarrhoea (7%), and hyperhidrosis (7%). In the ESC group, the TEAEs with an incidence ≥5% were: nausea (24%), headache (23%), nasopharyngitis (10%), dizziness (9%), dry mouth (9%), fatigue (8%), diarrhoea (8%), dyspepsia (6%), influenza (6%), hyperhidrosis (6%), somnolence (6%), and vomiting (6%). In the 24-week Treatment Period, the TEAEs with a statistically significantly higher incidence in the DUL group than in the ESC group were: dizziness (16% *versus* 9%), insomnia (13% *versus* 5%), and constipation (9% *versus* 3%). No TEAE had a statistically significantly higher incidence in the ESC group.
- In the Taper Period (Weeks 25 and 26), 19% of the patients in the DUL group and 20% of the patients in the ESC group had TEAEs. The TEAE with the highest incidence in the Taper Period was headache (DUL group: 4%, ESC group: 5%). There was no statistically significant difference between the treatment groups in the incidence of any TEAE in the Taper Period.
- In the Placebo Period (Week 27), 19% of the patients in the DUL group and 23% of the patients in the ESC group had TEAEs. The TEAE with the highest incidence in the Placebo Period was dizziness (DUL group: 8%, ESC group: 4%). There was no statistically significant difference between the treatment groups in the incidence of any TEAE in the Placebo Period.
- There were no clinically relevant changes within, or differences between treatment groups, in clinical safety laboratory tests, or vital signs.
- There were no statistically significant differences between the treatment groups in the change from Week 24 in DESS total score, or in the proportion of patients with a discontinuation syndrome (defined as a DESS total score increase ≥4).

Conclusions

- Based on the primary efficacy analysis, escitalopram 20 mg/day was as efficacious as duloxetine 60 mg/day in the long-term treatment of MDD.
- Based on the secondary efficacy analyses, escitalopram 20 mg/day was superior to duloxetine 60 mg/day in the acute treatment of MDD.
- Escitalopram 20 mg/day was superior to duloxetine 60 mg/day in improving patient daily function. Escitalopram 20 mg/day was as efficacious as duloxetine 60 mg/day in improving patient quality of life.
- Escitalopram 20 mg/day was better tolerated than duloxetine 60 mg/day, with fewer withdrawals due to adverse events during the 24-week Treatment Period.
- The proportions of patients with a discontinuation syndrome were similar after 24 weeks of treatment with escitalopram 20 mg/day or duloxetine 60 mg/day.

Date of the Report

10 September 2007

This study was conducted in compliance with the principles of *Good Clinical Practice*.