# Synopsis – Study 10796

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| **Title of Study**<br>A double-blind, randomised, multi-centre, fixed-dose study comparing the efficacy of escitalopram (20mg/day) with that of citalopram (40mg/day) in patients with Major Depressive Disorder |
| **Investigators**<br>33 investigators at 33 centres in 11 countries<br>*Signatory investigator* – Stuart Montgomery, Emeritus Professor of Psychiatry, Imperial College School of Medicine, University of London, London, United Kingdom |
| **Study Centres**<br>33 centres – 2 in Austria, 4 in Estonia, 10 in France, 1 in Hong Kong, 1 in Hungary, 2 in Malaysia, 1 in the Philippines, 4 in Poland, 1 in Singapore, 4 in Slovakia, and 3 in Turkey |
| **Publications**<br>None (as of the date of this report) |
| **Study Period**<br>*First patient first visit* – 17 January 2005<br>*Last patient last visit* – 10 October 2005<br>*Study terminated* – 5 May 2010 |
| **Objectives**<br>• *Primary objective*:<br>– to compare the efficacy of escitalopram (20mg/day) with that of citalopram (40mg/day) at the end of 8 weeks' treatment of outpatients with Major Depressive Disorder (MDD)<br>• *Secondary objectives*:<br>– to compare the efficacy of escitalopram (20mg/day) and citalopram (40mg/day) during the course of the study<br>– to evaluate the tolerability of escitalopram (20mg/day) and citalopram (40mg/day) during the course of the study<br>– to evaluate the proportion of patients on escitalopram or citalopram who are in remission at Week 8 (remission is defined as a MADRS total score ≤12)<br>– to evaluate the proportion of patients who respond to escitalopram or citalopram treatment at Week 8 and their time to response (response is defined as ≥50% decrease in MADRS total score from baseline) |

**Methodology**

- This was an interventional, multi-national, multi-centre, randomised, double-blind, parallel-group, active-comparator, fixed-dose study.
- The patients were outpatients recruited from specialist settings and selected general practitioners.
- The study consisted of the following periods:
  - *8-week Treatment Period* – the patients were randomised 1:1 at baseline to receive fixed doses of escitalopram or citalopram; the investigational medicinal products (IMPs) were administered as one tablet per day as follows:
    - escitalopram 20 mg/day – uptitrated; the starting dose was 10 mg/day for 7 days, and thereafter 20 mg/day from Day 8 up to Week 8
    - citalopram 40 mg/day – uptitrated; the starting dose was 20 mg/day for 7 days, and thereafter 40 mg/day from Day 8 up to Week 8
  - *optional Open-label Extension Period (France only)* – patients who had responded to treatment and who, as judged by the investigator, could benefit from continued treatment were offered open-label escitalopram 20 mg/day for 16 weeks, starting immediately after the 8-week Treatment Period
  - *Taper Period* – patients not eligible to participate in the optional Open-label Extension Period who completed the 8-week Treatment Period entered a 1-week, double-blind Taper Period; patients who completed the optional Open-label Extension Period entered a 1-week open-label Taper Period; patients who withdrew could, based on investigator's judgement, be offered taper IMP:
    - Patients randomised to escitalopram received escitalopram 10 mg/day for 7 days.
    - Patients randomised to citalopram received citalopram 20 mg/day for 7 days.
    - Patients who received open-label escitalopram received open-label escitalopram 10 mg/day for 7 days.
- Patients who completed the Taper Period, or withdrew and received taper IMP, were scheduled for a Safety Follow-up Visit 3 weeks after the last dose of taper IMP; patients who withdrew but did not receive taper IMP were scheduled for a Safety Follow-up Visit 4 weeks after the last dose of IMP.
- Efficacy was assessed at each visit in the 8-week Treatment Period; safety and tolerability were assessed at each visit.
- This study was paused after data had been published, which opened the discussion whether the possible scientific merit of continuing this study merely would be a replication of the already published findings. The study was paused for a significant amount of time, and was finally terminated, as it was considered that resuming the study activities was likely to introduce a high study population heterogeneity, and that the overall study quality would be negatively affected.

**Number of Patients Planned and Analysed**

- 500 patients were planned for enrolment: 250 in each treatment group
- For the Double-blind Period, patient disposition, patient disposition by centre, patient disposition by visit, withdrawals by primary reason, and withdrawals by all reasons are summarised in Tables 1, 2, 3, 4, and 5, respectively; withdrawals from the Double-blind Period by primary reason are presented in Listing 1
- For the Open-label Period, patient disposition, patient disposition by visit, and withdrawals by primary reason are summarised in Tables 6, 7, and 8, respectively; withdrawals from the Open-label Period by primary reason are presented in Listing 2.
- Patient disposition for the Double-blind Period is summarised below:

| | ESC | | CIT | | Total | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| **Patients randomised** | 117 | | 116 | | 233 | |
| **Patients treated (all-patients-treated set [APTS]):** | 117 | | 115 | | 232 | |
| Patients completed | 103 | (88.0) | 98 | (85.2) | 201 | (86.6) |
| Patients withdrawn | 14 | (12.0) | 17 | (14.8) | 31 | (13.4) |
| **Primary reason for withdrawal:** | | | | | | |
| Adverse event(s) | 10 | (8.5) | 9 | (7.8) | 19 | (8.2) |
| Lack of efficacy | 0 | (0.0) | 2 | (1.7) | 2 | (0.9) |
| Protocol violation | 1 | (0.9) | 4 | (3.5) | 5 | (2.2) |
| Withdrawal of consent | 1 | (0.9) | 0 | (0.0) | 1 | (0.4) |
| Lost to follow-up | 1 | (0.9) | 1 | (0.9) | 2 | (0.9) |
| Administrative or other reason(s) | 1 | (0.9) | 1 | (0.9) | 2 | (0.9) |
| **Analysis sets:** | | | | | | |
| APTS | 117 | | 115 | | 232 | |
| Full-analysis set (FAS) | 117 | | 114 | | 231 | |

Cross-references: Tables 1 and 4

- In the Open-label Period, 31 patients received treatment (*all-patients receiving open-label treatment set* [APOL]) and 27 completed; 4 (13%) patients withdrew, none due to adverse events (Table 8).

**Diagnosis and Main Inclusion Criteria**

Outpatients with a primary diagnosis of MDD according to DSM-IV-TR™ criteria (current episode confirmed using the Mini International Neuropsychiatric Interview [MINI], with a prior duration of ≥3 months and <2 years), who:

- had a Clinical Global Impression – Severity of Illness (CGI-S) score ≥5 at baseline
- had a Montgomery and Åsberg Depression Rating Scale (MADRS) total score ≥30 at baseline
- had a Sheehan Disability Scale (SDS) score ≥5 on at least one item at baseline
- were ≥18 and ≤65 years of age

**Investigational Medicinal Product, Dose and Mode of Administration, Batch Numbers**

*Escitalopram* – 20mg/day; tablets, orally; batch Nos. PS 2453 (10mg), 2023132 (10mg), 2032095 (20mg), 2028812 (20mg)

**Duration of Treatment**

8 weeks of double-blind treatment, 1 week of double-blind taper (not for patients who received open-label escitalopram); 16 weeks of open-label treatment (optional; France only), 1 week of open-label taper (only for patients who received open-label escitalopram; France only)

**Reference Therapy, Dose and Mode of Administration, Batch Numbers**

*Citalopram (Cipramil®)* – 40mg/day; tablets, orally; batch Nos. PS 2450 (20mg), PS 2460 (40mg), PS 2461 (40mg)

**Efficacy Assessments**

- *Primary variable*:
  - MADRS total score
- *Secondary variables*:
  - Hamilton Depression Scale – 24-item (HAM-$D_{24}$) score
  - Hamilton Depression Scale – 17-item (HAM-$D_{17}$) score
  - CGI-S score
  - Clinical Global Impression – Global Improvement (CGI-I) score
  - remission (MADRS total score ≤12)
  - response (≥50% decrease from baseline in MADRS total score)
  - SDS score

**Safety Assessments**

Adverse events (AEs)

**Statistical Methodology**

- 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 IMP (re-defined from definition in the *Statistical Analysis Plan* [SAP] to specify double-blind IMP)
  - *full-analysis set* (FAS) – all patients in the APTS who had at least one valid post-baseline assessment of the primary efficacy variable
  - *all-patients receiving open-label treatment set* (APOL) – all patients in the FAS who took at least one dose of open-label IMP (patients from French sites only; analysis set not specified in the SAP)
- For data presentation and analyses, the following periods were defined (periods not defined in the SAP):
  - *Double-blind Treatment Period* – from Baseline to the end of the 8-week Treatment Period
  - *combined Double-blind Taper and Safety Follow-up Periods* – from first to last dose of double-blind taper IMP plus the Safety Follow-up Period following the Double-blind Treatment Period
  - *Double-blind Period* – from Baseline to the end of the Safety Follow-up Period following the Double-blind Treatment Period
  - *Open-label Period* – from date of first dose of open-label escitalopram to the end of the Safety Follow-up Period following the optional Open-label Extension Period
  - *Entire Study Period* – from Baseline to the end of the Safety Follow-up Period following the optional Open-label Extension Period
- Exposure to IMP was summarised separately for the Double-blind Treatment Period, the combined Double-blind Taper and Safety Follow-up Periods, and the Open-label Period by duration (days), summary statistics (mean, median, standard deviation, minimum, and maximum), and total exposure (years).
- The limited number of patients enrolled resulted in insufficient data for the pre-specified analyses of efficacy, therefore no formal statistical analysis of efficacy was performed. The efficacy variables were summarised per visit (Double-blind Treatment Period only) using observed cases (OC).
- A statistical analysis was made on the proportion of patients with AEs, TEAEs, and SAEs in the Double-blind Treatment Period. A logistic regression model was specified adjusting for centre and treatment group. The analyses were performed as a two-sided test of the null hypothesis of no difference between treatment groups.
- The incidences of treatment-emergent adverse events (TEAEs; adverse events that began or changed in intensity after the first dose of double-blind IMP) were tabulated by system organ class (SOC) and preferred term and by preferred term for the Double-blind Treatment Period, and by preferred term for the combined Double-blind Taper and Safety Follow-up Periods and the Open-label Period.

**Demography of Study Population**

- Approximately two-thirds of the patients were women (range: 66% to 73%); the mean age was 41 years (range: 18 to 67 years; Table 9).
- The mean height, body weight, and body mass index at baseline were 167 cm (range: 142 cm to 187 cm), 69 kg (range: 36 kg to 135 kg), and 25 kg/$m^2$ (range: 15 kg/$m^2$ to 50 kg/$m^2$), respectively (Table 10).
- At baseline, there were no clinically relevant differences between the treatment groups with respect to medical history, physical examination findings, vital signs, or the use of concomitant medication (Tables 11, 12, 13, and 14, respectively).
- The mean baseline MADRS total score indicated that the patients had a current *severe* Major Depressive Episode (Table 18), and the distribution of CGI-S scores at baseline revealed that all patients were either *markedly* or *severely* ill (Table 25).

**Extent of Exposure**

- Exposure to IMP during the Double-blind Treatment Period, the combined Double-blind Taper and Safety Follow-up Periods, and the Open-label Period (by previous treatment group and total) is summarised in Tables 15, 16, and 17, respectively.
- During the Double-blind Treatment Period, the mean duration of exposure to escitalopram was 53 days (range: 2 to 71 days), and the total exposure to escitalopram was 17 years; the mean duration of exposure to citalopram was 54 days (range: 3 to 74 days), and the total exposure to citalopram was 16.7 years (Table 15).
- During the Open-label Period (by previous treatment group and total), the mean duration of exposure to escitalopram was 104 days (range: 24 to 137 days), and the total exposure to escitalopram was 8.8 years (Table 17).

**Efficacy Results**

- The efficacy variables are summarised per visit (FAS, OC) in Tables 18 to 39.
- Both treatment groups showed improvement in the mean scores of all the efficacy variables during the study.

**Safety Results**

• The adverse event incidences for the Double-blind Treatment Period are summarised below:

| | ESC | | CIT | |
|---|---|---|---|---|
| | n | (%) | n | (%) |
| Patients treated | 117 | | 115 | |
| Patients with treatment-emergent AEs (TEAEs) | 72 | (61.5) | 63 | (54.8) |
| Patients who died | 0 | (0.0) | 0 | (0.0) |
| Patients with serious AEs (SAEs) | 3 | (2.6) | 2 | (1.7) |
| Patients with AEs leading to withdrawal | 10 | (8.5) | 9 | (7.8) |
| Patients with baseline AEs | 1 | (0.9) | 3 | (2.6) |
| Total number of TEAEs | 170 | | 150 | |
| Total number of SAEs | 3 | | 2 | |
| Total number of baseline AEs | 1 | | 3 | |

Cross-reference: Table 40

• The adverse event incidences for the combined Double-blind Taper and Safety Follow-up Periods are summarised below:

| | ESC | | CIT | |
|---|---|---|---|---|
| | n | (%) | n | (%) |
| Patients treated | 99 | | 100 | |
| Patients with TEAEs | 3 | (3.0) | 5 | (5.0) |
| Patients with SAEs | 0 | (0.0) | 0 | (0.0) |
| Patients with AEs leading to withdrawal | 0 | (0.0) | 0 | (0.0) |
| Total number of TEAEs | 3 | | 10 | |

Cross-reference: Table 41

• The adverse event incidences (by previous treatment group and total) for the Open-label Period are summarised below:

| | ESC | | CIT | | Total | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Patients treated | 17 | | 14 | | 31 | |
| Patients with TEAEs | 1 | (5.9) | 2 | (14.3) | 3 | (9.7) |
| Patients with SAEs | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Patients with AEs leading to withdrawal | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Total number of TEAEs | 1 | | 3 | | 4 | |

Cross-reference: Table 42

**Safety Results – continued**

- No deaths occurred during the study.
- A total of 5 patients had SAEs: 3 in the escitalopram group and 2 in the citalopram group; all the SAEs occurred during the Double-blind Treatment Period (Table 43 and Listing 3).
- None of the SAEs occurred in >1 patient in either treatment group. One SAE was considered *related* to IMP (*circulatory collapse* [citalopram group]; Listing 3). For further details, see *Narratives of Serious Adverse Events*.
- A total of 19 patients had adverse events leading to withdrawal: 10 in the escitalopram group and 9 in the citalopram group; all adverse events leading to withdrawal occurred during the Double-blind Treatment Period (Table 44 and Listing 4).
- With the exception of *diarrhoea* (2 patients in the escitalopram group) and *depression*, *dizziness*, and *nausea* (2 patients each in the citalopram group), no adverse event led to withdrawal in >1 patient in either treatment group (Listing 4).
- There were no statistically significant differences between the treatment groups with respect to the proportions of patients with adverse events, TEAEs or SAEs in the Double-blind Treatment Period (Table 45).
- The majority of the patients had TEAEs that were considered by the investigator to be *mild* or *moderate* (Listing 5). A total of 15 patients had *severe* TEAEs: 12 in the escitalopram group and 3 in the citalopram group. All *severe* TEAEs occurred during the Double-blind Treatment Period. With the exception of *insomnia* (3 patients in the escitalopram group), no *severe* adverse event occurred in >1 patient in either treatment group.
- TEAEs in the Double-blind Treatment Period are presented by SOC and preferred term in Table 46 and by preferred term in Table 47. The SOCs with the highest incidences (≥15%) of adverse events in either treatment group were:
  - *gastrointestinal disorders* (escitalopram group: 26% [mainly due to *nausea* and *dry mouth*]; citalopram group: 30% [mainly due to *nausea*])
  - *nervous system disorders* (escitalopram group: 23% [mainly due to *headache*]; citalopram group: 22% [mainly due to *headache*])
  - *psychiatric disorders* (escitalopram group: 17% [mainly due to *insomnia*]; citalopram group: 15% [mainly due to *insomnia* and *tension*])
- The following TEAEs had an incidence ≥5% in either treatment group during the Double-blind Treatment Period:

| Preferred Term | ESC | | CIT | |
|---|---|---|---|---|
| (MedDRA Version 12.1) | n | (%) | n | (%) |
| Headache | 15 | (12.8) | 14 | (12.2) |
| Nausea | 11 | (9.4) | 20 | (17.4) |
| Dry mouth | 9 | (7.7) | 5 | (4.3) |
| Insomnia | 9 | (7.7) | 5 | (4.3) |
| Dizziness | 8 | (6.8) | 6 | (5.2) |
| Ejaculation delayed (sex specific) | 2 | (6.3) | 4 | (10.3) |
| Diarrhoea | 6 | (5.1) | 5 | (4.3) |
| Somnolence | 4 | (3.4) | 7 | (6.1) |
| Decreased appetite | 1 | (0.9) | 6 | (5.2) |

Cross-reference: Table 47

- TEAEs in the combined Double-blind Taper and Safety Follow-up Periods are presented by preferred term in Table 48.
- TEAEs in the Open-label Period (by previous treatment group and total) are presented by preferred term in Table 49.

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| **Conclusions**<br>• Both treatment groups showed improvement in the mean scores of all the efficacy variables during the study.<br>• Both escitalopram and citalopram were safe and well tolerated. The adverse events were consistent with the known safety profiles of escitalopram and citalopram. |
| **Date of the Report**<br>11 April 2011 |
| This study was conducted in compliance with the principles of *Good Clinical Practice*. |