## Title of Study

An open multicentre prospective study assessing the safety and efficacy of escitalopram 10 to 20mg/day, as continuation treatment of citalopram intravenous in patients suffering from Major Depressive Disorder

## Study Centres

49 centres in France

## Study Period

First patient first visit – 22 Nov 2002  
Last patient last visit – 14 Aug 2003

## Objectives

- **Primary objective:**
  - to evaluate the safety of oral escitalopram, 10 to 20mg daily, in patients with Major Depressive Disorder (MDD) who have been treated with citalopram intravenous (i.v.), (20mg or 40mg daily) for at least 4 days. The patients were switched to oral escitalopram the day after the last day of the citalopram i.v. period

- **Secondary objectives:**
  - to evaluate the efficacy in the subgroups of depressive patients treated daily with 10mg or 20mg of escitalopram. Assessment of efficacy was based on the Montgomery Åsberg Depression Rating Scale (MADRS) total score change from baseline
  - to evaluate the efficacy in subpopulations of patients defined according to their previous depressive history: single or recurrent episode(s), resistant depression, or chronic depression, based on the MADRS total score change from baseline
  - to evaluate the possible correlation between the changes for the Clinical Global Impression – Global Improvement (CGI-I) and the Patient Global Evaluation (PGE) over the 6-week treatment period

## Methodology

- Open label, multicentre, prospective study.
- Patients who provided written informed consent and who fulfilled all the inclusion criteria and none of the exclusion criteria were included in the study.
- The patients were treated according to the recommendations given in the Summary of Product Characteristics (SPC).
- Patients were assessed on 4 occasions, at inclusion visit (last day of citalopram i.v. administration = baseline) and at 3 visits: at Days 3, 15, and 42. Citalopram i.v. and the first oral escitalopram dose were administered to hospitalized patients, most of whom were subsequently treated as outpatients.
- At visit on Day 3, the investigator could increase the dose from 10 to 20mg/day if this was considered necessary by the investigator. Thereafter, the dose of escitalopram was kept fixed until the end of the study.
Number of Patients Planned and Analysed
- Approximately 240 patients were planned.
- Patient disposition is tabulated below:

<table>
<thead>
<tr>
<th>Escitalopram 10-20mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>n 173</td>
</tr>
<tr>
<td>(%)</td>
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</table>

<table>
<thead>
<tr>
<th>Patients enrolled</th>
<th>173</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients treated (APTS):</td>
<td>171</td>
</tr>
<tr>
<td>Intent-to-treat (ITT):</td>
<td>170</td>
</tr>
<tr>
<td>Patients completed</td>
<td>147 (85)</td>
</tr>
<tr>
<td>Patients withdrawn</td>
<td>26 (15)</td>
</tr>
</tbody>
</table>

Primary reason for withdrawal:
- Adverse events (AEs)
- Lack of efficacy

n = number of patients; % = percentage of patients enrolled

Diagnosis and Main Selection Criteria
Patients who:
- gave their signed informed consent
- were male or female patients
- were ≥18 years of age
- had had a diagnosis of MDD established at the time when citalopram i.v. was prescribed (diagnosis confirmed retrospectively with a neuropsychiatric interview)
- had been treated with citalopram i.v. (20mg or 40mg daily) for at least 4 days prior to the switch to escitalopram
- Female patients of childbearing potential used adequate contraception (as judged by the investigator) at inclusion and during the study.

Investigational Product, Dose and Mode of Administration
Escitalopram – 10 or 20mg once daily; orally

Duration of Treatment
6 weeks

Reference Therapy, Dose and Mode of Administration
None

Criteria for Evaluation – Efficacy
- Primary variable:
  - none, the primary objective was to evaluate safety of oral escitalopram
- Secondary variables:
  - MADRS total score change from baseline
  - efficacy defined according to the patient’s previous depressive history: single or recurrent episode(s), resistant depression or chronic depression, based on MADRS total score change from baseline
  - the possible correlation between the changes for the CGI-I and PGE over the 6-week treatment period

Criteria for Evaluation – Safety
AEs
### Statistical Methods

#### Efficacy
- The efficacy analysis was carried out on all patients from the efficacy population which included patients who took at least one dose of study medication and who had at least one valid post-baseline assessment of the primary efficacy variable (n=170).
- Efficacy analysis MADRS change from baseline to end of treatment was refined by subgroup analyses by severity of depressive symptoms at inclusion (MADRS score <30 or ≥30) and type of depressive episode (isolated or recurrent).
- Estimation of the proportion of responders defined as an improvement of at least 50% in MADRS score or by a CGI-I score of 1 or 2.
- Estimation of the proportion of remitters defined as MADRS ≤12.
- Missing data and withdrawn patients were handled by the method of last observation carried forward (LOCF).
- All statistical tests were 2-tailed, and a probability level of 0.05 was considered to be statistically significant.
- The correlation between mean scores on the CGI-I and PGE was assessed at each visit as a function of the nature and severity of the initial depressive episode (Spearman rank coefficient).

#### Safety
- The safety analysis was carried out on all patients in the safety population and consisted of all included patients who took at least one dose of study medication (n=171).
- The primary safety parameter was the number and frequency of AEs over the 6-week treatment period.

### Demography of Study Population
- The mean age was 47 ± 10 years (range 19 to 77), and the majority of patients were female (122; 71%).
- The depressive episode was recurrent in the majority of cases with a mean duration at inclusion of 5 months.
- In the overall population, the mean score on the MADRS scale at inclusion was 31.6 and was ≥30 in 110 patients (65%), indicative of severe depression.
- After visit at Day 3, 80 patients (47%) were treated with escitalopram 10mg/day and 91 (53%) received escitalopram 20mg/day.

### Efficacy Results
- Change in MADRS total score from baseline to each visit was statistically significant (p <0.0001) and was similar for the escitalopram 10mg and escitalopram 20mg groups.
- Change in MADRS mean total score from baseline to each visit for single or recurrent episodes was statistically significant (p <0.0001). The change in MADRS mean total score from baseline to each visit was statistically significant (p <0.01) for chronic depression. The change in MADRS total score from baseline to Visits 3 and 4 was statistically significant (p <0.05) for resistant depression.
- Subgroup analysis showed that the mean MADRS score at inclusion was slightly higher (32.1) in patients presenting recurrent compared to isolated (29.6) depressive episodes.
- A total of 67% of the patients were considered responders, and 95% patients were considered to be in remission (MADRS criteria) at study end.
- The proportion of patients who had improved according to the CGI-I increased over the study period; at the end of study visit the mean CGI-I was 2.3 and most of the patients (68%) had a CGI-I score of ≤2, corresponding to much to very much improved. The proportion of responders using the CGI-I criteria was greatest in the subgroup of patients with severe depression at inclusion (MADRS score ≥30) and treated at a dose of 20mg/day (n=47/60; 78%).
- The proportion of patients considering themselves improved or very much improved at study end on the PGE questionnaire (score of ≤2) was 58%. The mean PGE score at study end was 2.5.
- A significant correlation was observed between scores on the CGI-I and the PGE at each visit (Spearman rank coefficients of 0.59 on Day 3, 0.71 on Day 15, and 0.79 on Day 42; p<0.001) irrespective of the nature of the depressive episode (p<0.005) and of initial symptom severity (p<0.01).
Safety Results

- A total of 57 patients (33%) experienced AEs during the study; 21 patients (12%) in the escitalopram 10mg group, and 36 patients (21%) in the escitalopram 20mg group. Of these, 11 patients (6%) experienced severe AEs. A total of 6 patients (4%) experienced serious AEs (SAEs) during the study.
- For a total of 16 patients with at least one AE, the AEs were judged as probably related to study medication, and for 29 patients as possibly related to study medication.
- The most frequently reported AEs in the escitalopram 20mg group were anxiety (10 patients; 6%), insomnia (7 patients; 4%), nausea (5 patients; 3%), and headache, diarrhoea and depression aggravated (3 patients; 2%). In the 10mg group AEs reported by more than one patient were mouth dry and anxiety (4 patients; 2%), and asthenia (3 patients; 2%).
- Overall, AEs were most commonly reported in the psychiatric disorders system organ class (SOC) with anxiety being the AE mostly reported.
- A total of 7 patients were withdrawn from the study due to AEs (4 patients in the escitalopram 10mg group and 3 patients in the escitalopram 20mg group). One patient in the escitalopram 20mg group was withdrawn due to an AE (somnolence) of severe intensity.
- Mean time to onset of AEs had the shortest duration (8.29 ± 7.62 days) in the escitalopram 10mg group compared to the escitalopram 20mg group (11.28 ± 13.55 days). Mean time to withdrawal of AEs had the shortest duration (10.25 ± 7.59 days) in the escitalopram 10mg group compared to the escitalopram 20mg group (23.67 ± 17.67 days).
- The AE incidence for 10 to 20 mg escitalopram is summarised below, including AEs with an incidence ≥5%.

<table>
<thead>
<tr>
<th>Escitalopram 10-20mg</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients who died</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Patients with SAEs</td>
<td>6</td>
<td>(4)</td>
</tr>
<tr>
<td>Patients with AEs</td>
<td>57</td>
<td>(33)</td>
</tr>
<tr>
<td>AEs with an incidence ≥5%:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>anxiety</td>
<td>15</td>
<td>(9)</td>
</tr>
<tr>
<td>insomnia</td>
<td>8</td>
<td>(5)</td>
</tr>
</tbody>
</table>

n = number of patients; % = percentage of APTS

Publication


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