Clinical Trial Report Summary – Study 99812

Title of Study
An open multicenter prospective randomised study assessing the impact of treatment information on treatment outcome and testing biochemical and symptom-related response predictors in depressed outpatients treated with escitalopram

Study Centres
59 centres in Sweden

Study Period
First patient first visit – 8 March 2003
Last patient last visit – 9 June 2004

Objectives
• Primary objective:
  – to assess the impact of detailed treatment information on depression in outpatients treated with escitalopram for 24 weeks
• Secondary objectives:
  – to evaluate if the body mass index (BMI) and waist circumference (WC) correlate to clinical response
  – to evaluate if serotonin (WB-5HT) and L-tryptophan concentrations in whole blood (WB-TRP) correlate to clinical response

Methodology
• 24-week, open-label, multicentre, prospective, randomised study.
• Patients ≥18 years of age suffering from an acute episode of depression requiring pharmacological treatment were enrolled (as outpatients) and treated according to the recommendations in the Summary of Product Characteristics (SPC) for escitalopram.
• The usual recommended starting dose of escitalopram is 10mg/day:
  – Depending on individual patient response, the dose could be increased to a maximum of 20mg/day.
• Five treatment visits were planned, at baseline (Week 0) and Weeks 2, 6, 12, and 24.
  – BMI and WC were measured at baseline.
  – In addition, WB-5HT and WB-TRP were measured in a subgroup of approximately 20% of patients at baseline and Week 1 at certain centres equipped to collect blood samples.
• Patients were randomised to 2 groups:
  – a) patients receiving general treatment information (standard information group) and
  – b) patients receiving more detailed treatment information (extended information group)
• The standard information group received the usual information about depression and treatment strategy and the only side effect mentioned was nausea.
• The extended information group received the same information, but in more detail, including a long list of all possible side effects as well as other potential risks.
Number of Patients Planned and Analysed
• Approximately 560 patients were planned to be enrolled.
• Patient disposition is tabulated below:

<table>
<thead>
<tr>
<th></th>
<th>Extended information</th>
<th>Standard information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients randomised: Total number = 333</td>
<td>162</td>
<td>169</td>
</tr>
<tr>
<td>Patients treated (APTS)</td>
<td>158</td>
<td>165</td>
</tr>
<tr>
<td>Intent-to-treat (ITT)</td>
<td>152</td>
<td>160</td>
</tr>
<tr>
<td>Patients completed</td>
<td>129</td>
<td>140</td>
</tr>
<tr>
<td>Patients withdrawn</td>
<td>29</td>
<td>25</td>
</tr>
</tbody>
</table>

Primary reason for withdrawal
- Adverse events (AEs) 13 (8.2) 6 (3.6)
- Lack of efficacy 2 (1.3) 4 (2.4)

Diagnosis and Main Selection Criteria
Outpatients who:
• were suffering from acute episode of depression requiring pharmacological treatment according to the SPC for escitalopram
• gave their signed informed consent
• were ≥ 18 years of age

Investigational Product, Dose and Mode of Administration
Escitalopram – 10 mg once daily with the possibility of decreasing to 5mg or increasing to a maximum of 20mg; orally

Duration of Treatment
24 weeks

Reference Therapy, Dose and Mode of Administration
None

Criteria for Evaluation – Efficacy
• Primary variable:
  – Montgomery Åsberg Depression Rating Scale (MADRS) total score
• Secondary variables:
  – Clinical Global Impression – Severity of Illness (CGI-S)
  – Clinical Global Impression – Global Improvement (CGI-I)
  – Patient Global Evaluation (PGE)
• Other measurements:
  – BMI
  – WC
  – WB-5HT
  – WB-TRP

Criteria for Evaluation – Safety
AEs
Statistical Methods

Efficacy

• The following analysis set was used:
  – intent-to-treat (ITT) – all patients who took at least one dose of investigational medicinal product (IMP) and who had at least one valid post-baseline assessment of the primary efficacy variable.
• The analyses were performed using the last observation carried forward (LOCF) approach.
• Primary efficacy analysis:
  – Change in MADRS total score from baseline to completion or last assessment was analysed using an analysis of covariance (ANCOVA) model with baseline MADRS score as covariate and treatment group as factor.
• Secondary efficacy analyses:
  – Change in the CGI-S score was performed in a similar manner to the MADRS total score.
  – The CGI-I and PGE scores were summarised at Visits 2, 3, 4, and the completion/withdrawal visit for each treatment group.
  – Possible correlations during the 24 weeks of treatment were calculated using Spearman’s rank-order correlation coefficient between the variations of the CGI-I and PGE and its associated probability.

Safety

• All safety analyses were based on the:
  – all-patients-treated set (APTS) – all patients who took at least one dose of IMP.
• Correlation between MADRS change from baseline to the completion/withdrawal visit and BMI, WC at baseline.
• Correlation between MADRS change from baseline to the completion/withdrawal visit and WB-5HT and WB-TRP baseline values and WB-5HT and WB-TRP change from baseline (for approximately 20% of the patients).
• Logistic regression was used to try to identify factors (baseline BMI, WC) predictive of the response to treatment (responders versus non-responders).
• The same analysis with BMI, WC, WB-5HT and WB-TRP baseline values and WB-5HT and WB-TRP change to Visit 1B as prognostic factors was performed (for approximately 20% of the patients).

Demography of Study Population

• The mean age was 48 ± 16 years (range 18 to 99) and two thirds (66%) of the patients were female.
• Baseline MADRS total score was 26.8 ± 7.4 in the extended information group and 27.6 ± 6.8 in the standard information group.
• Both groups and the distribution/range in BMI was similar in point baseline.

Efficacy Results

• MADRS
  – MADRS total scores decreased from baseline to the final visit in both treatment groups, with no difference between the two groups.
  – At the final visit, 78% of the patients were responders (≥50% decrease from baseline in the MADRS total score) with no differences between the groups.
  – Remission (MADRS total score ≤12) was achieved by 72% of the patients by the final visit, with no difference between groups.
• CGI-S and CGI-I
  – The mean CGI-S scores decreased during the study from 4.0 ± 0.7 to 2.1 ± 1.2.
  – Mean CGI-I scores showed a continuous reduction during the study. At the last visit (completion/withdrawal), 70% of the patients were responders (CGI-I = 1 or 2).
  – There were no differences between the two treatment groups.
Efficacy Results – continued

• PGE scores
  – PGE scores decreased progressively indicating that patients had a progressive and continued improvement in symptoms.
  – The correlation investigated between CGI-I and PGE was statistically significant at all time points, indicating that both investigators and patients considered that symptoms of depression improved with escitalopram treatment.

• BMI and WC
  – Neither baseline BMI nor WC correlated with the change in the MADRS total score from baseline to the final visit, with a Spearman’s rank-order correlation coefficient of 0.0286 (p=0.618) for BMI, and a Spearman’s rank-order correlation coefficient of -0.0056 (p=0.923) for WC.

• WB-5HT and WB-TRP
  – Mean WB-5HT and WB-TRP values were similar in both treatment groups at baseline.
  – WB-5HT values decreased by over 50% over the first week of treatment while WB-TRP increased by 10% over the same period.
  – There was no correlation in response to escitalopram (decrease from baseline in MADRS total score to last assessment) and either baseline WB-5HT or WB-TRP levels or the changes of these values during the first week.

Safety Results

• Escitalopram was safe and well tolerated.
• In this study, 17 patients reported an SAE - aggravated depression (n=2), transient ischaemic attack (n=2), and 1 patient with each of the following: cellulitis, anaphylactoid reaction, cardiac failure, grand mal convulsions, flaccid paralysis, lupus erythematosus, atrial fibrillation, gastric carcinoma, pulmonary embolism, psychosis, abscess, pharyngitis, surgery, malignant melanoma, and urinary tract infection. There were no deaths in this study.
• The AE incidence is summarised below:

<table>
<thead>
<tr>
<th></th>
<th>Extended information</th>
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</thead>
<tbody>
<tr>
<td>Patients who died</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Patients with serious AEs (SAEs)</td>
<td>8 (61.4)</td>
<td>9 (63.6)</td>
</tr>
<tr>
<td>Patients with AEs</td>
<td>97 (61.4)</td>
<td>105 (63.6)</td>
</tr>
</tbody>
</table>

n = number of patients; % = percentage of patients

• AEs with an incidence ≥5% is summarised below:

<table>
<thead>
<tr>
<th></th>
<th>Extended information</th>
<th>Standard information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with AEs</td>
<td>97 (61.4)</td>
<td>105 (63.6)</td>
</tr>
<tr>
<td>nausea</td>
<td>31 (19.6)</td>
<td>23 (13.9)</td>
</tr>
<tr>
<td>headache</td>
<td>21 (13.3)</td>
<td>18 (10.9)</td>
</tr>
<tr>
<td>sweating increased</td>
<td>11 (7.0)</td>
<td>16 (9.7)</td>
</tr>
<tr>
<td>fatigue</td>
<td>16 (10.1)</td>
<td>10 (6.1)</td>
</tr>
<tr>
<td>anxiety</td>
<td>8 (5.1)</td>
<td>16 (9.7)</td>
</tr>
<tr>
<td>dizziness</td>
<td>8 (5.1)</td>
<td>12 (7.3)</td>
</tr>
</tbody>
</table>

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


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