Studie 043

(Z2020 0043)

Studienbericht

Abbreviated Study Report Final version

Z2020 0043

Previous Reports of the Study:
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It is the policy of Pharmacia & Upjohn to conduct clinical trials in compliance with company SOPs and Standards which incorporate the requirements of the ICH Guideline for Good Clinical Practice. These include trial conduct and archiving of essential documents. Protocol deviations are described in this report.

Trial Initiation Date	1999-09-01
Trial Completion Date	2001-05-16
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Development Phase of Trial	IV
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Date of the Report	2003-01-20

1 SIGNATURE PAGE

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2 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

A total of 39 investigators participated in this trial at 23 centers in the Sweden (12), Denmark (7), and Finland (4). A list of the investigators and their affiliations are located in the master file at Pharmacia, MC Sweden. Curriculum vitaes for each are located in the master file at the Market Companies.

Laboratory tests were performed at local clinical laboratories, all certified according to current ISO standard.

3 SYNOPSIS

Name of Company: Pharmacia Corporation **Name of Finished Product:** EDRONAX **Name of Active Ingredient:** Reboxetine mesylate	**Individual study table**	(For National authority use only)

Title of study:
Efficacy and tolerability of reboxetine (PNU-155950E) compared to citalopram in a double-blind study in patients with Major Depressive Disorder.

Protocol number:
Z2020 0043

Investigators and Study Centers:
The study was conducted at 23 study centers, including 12 centers in Sweden, 7 in Denmark, and 4 in Finland.

Publication (reference):
None

Studied period (years):
Date of first enrollment: 1999-09-11
Date of last patient visit: 2001-03-13

Phase of development:
IV

Objectives

Primary:
To assess efficacy and tolerability of reboxetine in comparison with citalopram in patients suffering from Major Depressive Disorder (MDD) as determined by absolute change from baseline in the Hamilton Rating Scale for Depression (HAM-D, 21 items).

Secondary:
To assess efficacy of reboxetine in comparison with citalopram in patients suffering from MDD as determined by the Montgomery-Asberg Depression Rating Scale (MADRS), Clinical Global Impression (CGI), Social Adaptation Self-evaluation Scale (SASS) scales, and the Sexual function (SF) scales.

Methodology:
This phase IV, multicenter, randomized, double-blind, active-controlled, parallel group study was conducted in 359 patients (intent-to-treat [ITT] population) aged 16 to 71 years who suffered from MDD without psychotic features, as diagnosed using criteria defined by the Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition (DSM-IV). Written informed consent was obtained for each patient prior to entry into the study. Patients were required to have a screening total score of ≥22 on the 21-item HAM-D that was confirmed at the baseline visit after an appropriate washout period based on the type of previously used psychoactive medication(s). Eligible patients were randomized to receive 24 weeks of treatment with reboxetine (8 mg/day, days 0-27; 8-10 mg/day, days 28-154) or citalopram (20 mg/day, days 0-27; 20-40 mg/day, days 28-154). The optional dose increase to 10 mg/day of reboxetine or 40 mg/day of citalopram was allowed after 4 weeks of therapy in those patients whom the investigator believed would benefit in terms of response and would adequately tolerate the increased dose. Study visits were conducted at baseline, week 2, 4, 6, 12, 18 and 24 or after drop-out. Efficacy and safety measures were assessed at every visit.

Number of patients (planned and analyzed):

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300 planned (86% power to detect a group difference of 2.5 or more in HAM-D score. 359 patients were randomised, 357 received treatment (181 reboxetine, 176 citalopram), and were included in the safety analysis, while 350 were included in the FAS-analysis (efficacy etc).

Diagnosis and main criteria for inclusion:

Male or female subjects ≥18 and ≤70 years of age* who had a diagnosis of major depressive disorder (MDD) (without psychotic features, dysthymic or cyclothymic disorder, bipolar I or bipolar II disorders, substance-related disorders, schizophrenia, other psychotic disorders, or MDD associated with endocrine disorders) as defined by DSM-IV were eligible for the trial. Patients must have a screen and baseline HAM-D total score of ≥22. Patients must not have any medical complication or physical finding that could interfere with study activities or drug absorption, distribution, metabolism or excretion; a history of electroconvulsive therapy within the previous 6 months; hypersensitivity or a lack of response to a previous course of reboxetine or citalopram; or a positive serum pregnancy test or breast feeding. Patients could not take any psychotropic medications (other than protocol-specified sedatives/hypnotics that could be taken on an as-needed basis for sleep) or any medications that are known to inhibit major drug-metabolizing enzymes (other than cytochrome p450-2D6) or vitamin K-dependent coagulation factors.

* Local amendment, age 16-71 years.

Test product, dose and mode of administration

Reboxetine was supplied as capsules containing PresTabs in strengths of 2 or 4 mg. From baseline through week 4 (days 0 to 27) reboxetine was administered in twice-daily doses of 4 mg, for a total of 8 mg daily. After 4 weeks of treatment (days 28 through 154), an optional increase to 10 mg/day was available with patients taking a 6-mg dose in the morning and a 4-mg dose in the late afternoon.

Reference therapy, dose and mode of administration:

Citalopram was manufactured by H. Lundbeck A/S and repackaged as capsules in strengths of 20 or 40 mg. From baseline through week 4 (days 0 to 27), citalopram was administered in a morning dose of 20 mg/day. After 4 weeks of treatment (days 28 through 154), an optional increase to 40mg/day was available with patients taking a 40-mg dose in the morning. Placebo capsules consisting of lactose-filled gelatin capsules were administered in the afternoon to maintain the study blind.

Duration of treatment:

Patients were to be treated for a total of 24 weeks unless, in the opinion of the investigator, it was medically necessary or the wish of the patient to withdraw from treatment. A post-study tail off period of 2 weeks was recommended.

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Efficacy evaluation:

The primary efficacy endpoint was the absolute change from baseline in the 21-Item HAM-D total score.

Secondary efficacy variables were: SASS change in total score, MADRS change in total score, CGI score, response rate (reduction of at least 50% in HAM-D 21 total score from baseline), remission rate (HAM-D 21 total score of 10 or less at each post-baseline visit), time to response, i.e. reduction of at least 50% in HAM-D 21 total score from baseline, days from baseline, and time to remission, i.e. HAM-D 21 total score of 10 or less, days from baseline.

Safety:

Treatment emergent symptoms (TES; spontanous and via the UKU scale), physical examinations, and laboratory assays were used to monitor patient safety.

Statistical methods:

For the continuous variables (i.e. HAM-D total, MADRS and SASS total), testing for difference between 2 treatment groups was performed using a 2-way analysis of variance (ANOVA) model that included treatment, investigator, age, and baseline terms. A group difference of 2.5 or more in HAM-D total score was assessed to be clinically significant. Treatment-by-center interaction was explored and included if it contributed significantly to the model. The response variables were to be the change from baseline scores at each visit. Categorical data (i.e. response and remission) were analyzed by Cochran-Mantel-Haenszel (CMH) test. In addition to p-values, 95% confidence intervals for the difference between 2 treatment groups were also computed for HAM-D total mean change from baseline, SASS total mean change from baseline, response rate, and remission rate. Two types of analyses should be performed for the primary variable i.e. HAM-D 21 total score: “last observation carried forward” (LOCF) and “observed cases” (OC). The LOCF analysis uses the last valid assessment as an estimate for all subsequent missing values. The OC analysis does not replace missing data. The LOCF was to be regarded as the primary analysis and the OC was to be secondary. When data was analysed it was concluded that the LOCF analysis was less valid since there was a huge amount of missing data. Another reason for not using the LOCF was that the treatment effect was increasing over time, which would have been ignored in an LOCF analysis. The OC was therefore considered as the most valid analysis for the primary efficacy variable.

Final study population and withdrawals

Of the 357 subject receiving study medication, 350 were included in the efficacy analysis, i.e. provided efficacy data at the visit week 2. During the study period 145 subjects were withdrawn, 91 in the reboxetine group and 54 in the citalopram group. The main reasons for withdrawal were: AE’s, “patient’s own decision”, missing visit or unsatisfactory effect. The higher drop-out rate in the reboxetine group means that the treatment groups were unbalanced with respect to number of patients at the end of the study. 93 reboxetine patients and 123 Citalopram patients completed the 24 weeks visit. Of the patients evaluable for safety analysis, the percentage of patients who discontinued treatment due to adverse events at any time during the treatment period was higher in the reboxetine group (19.9%; 36/181) than in the citalopram group (5.1%; 9/176). Most of the reboxetine patients that discontinued due to adverse events did so during the first 2 weeks of treatment

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Efficacy results:

The primary endpoint was the change in HAM-D 21 from baseline to week 24. Observed case (OC) analysis showed no significant differences between the two treatments in any of the efficacy parameters. LOCF analysis, however, showed a greater reduction of the HAMD scores with citalopram compared with reboxetine (–19.6 vs –17.8; p=0.034). The analysis of change in HAM-D 21 from baseline was also performed for a number of subgroups (gender, HAM-D 21 severity at baseline, CGI severity at baseline. The subgroup analyses did not identify any statistically significant differences between the treatments.
According to the OC analysis, the mean change in MADRS from baseline to week 24 was –23.2 in both treatment groups, while the LOCF showed a change of –18.1 for reboxetine and –20.6 for citalopram. For CGI, mean change from baseline was –5.0 in both groups (OC). The mean change in SASS total score from baseline to week 24 was 9.1 for reboxetine and 9.2 for citalopram (OC). The difference was not statistically significant. Neither did a subgroup analysis of responders show any statistically significant difference between the two treatment groups.
No statistically significant difference in response rate was detected (p=0.1215 and p=0.0577; OC and LOCF, respectively). About 90% of the patients in both groups were responding to the treatment at the week 24 visit. In remission rate, a statistically significant difference in favour of citalopram was identified at the 24 weeks visit (p=0.0166 and p=0.0032, OC and LOCF, respectively). 79% of the reboxetine-treated patients and 87% of the citalopram-treated patients were in remission at the 24 weeks visit.

Safety results:

The number of TES was 185 in the reboxetine group compared to 155 in the citalopram group. These TES occurred in 51% of the reboxetine patients and 40% of the citalopram patients. The most frequently reported adverse event among the reboxetine-treated patients were: dry mouth (15.7%), constipation (12.2%), tendency of sweating (11%), decreased sleep (7.1%), nausea (5.8%), increased dream activity (5,7%), headache (5.7%), orthostatic dizziness (5.2%), and micturation disturbances (5.2%). In the citalopram group, the most frequently reported adverse events were: orgastic dysfunction (13.2%), nausea (7.1%), dizziness (5.6%), and influenza like symptoms (5.1%). The majority of adverse events reported by patients in both treatment groups were mild to moderate in intensity.

In the reboxetine group, the prevalence of anorgasmia among women decreased over the study period, while corresponding prevalence increased in the citalopram group. Among sexually active men, the prevalence of delayed ejaculation decreased over time in the reboxetine group, but increased in the citalopram group.

No deaths were reported during this study. Serious adverse events were reported in 4 reboxetine-treated patients and 4 citalopram-treated patients. In the reboxetine group: 2 suicidal attempts, 1 abdominal pain, and 1 hypertension. In the citalopram group: 2 suicidal attempts, 1 pregnancy unintended and 1 alcohol problems.

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CONCLUSIONS:
According to the sample size calculations 150 patients were needed in each treatment group. However only 93 reboxetine treated patients and 123 citalopram treated patients were included in the primary efficacy analysis. This fairly large drop-out rate in combination with the loss of statistical power may jeopardize the validity of the study. . According to the OC analysis, there was no statistically significant difference in the primary efficacy variable (change in HAM-D 21 score at week 24) between the two treatments. The LOCF analysis showed a somewhat greater reduction of the HAM-D scores with citalopram. Due to the high number of early drop-outs in the reboxetine group, and the long duration of the study, the OC analysis was judged to be the most appropriate technique. Baseline data and demographics were well balanced between the treatment groups, meaning that the descriptive statistics indicated equivalent groups regarding prognostic factors such as age, gender and HAM-D total score. The number of TES was 185 in the reboxetine group compared to 155 in the citalopram group. There were 4 serious TES in each treatment group, and none of them was judged to be drug related. The adverse-event profile that was observed for reboxetine in this study is consistent with the profile that was established in the clinical study database. Sexual dysfunction was significantly more common in the citalopram group than in the reboxetine group. The number of drop outs was high in both treatment groups, especially in the reboxetine group. Most of the reboxetine patients that discontinued due to adverse events did so during the first weeks of treatment, probably due to an un-titrated reboxetine starting dose of 8 mg per day. No new safety concerns associated with the use of reboxetine were identified.

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APPENDICES

Appendix 1. Demographic Data

Appendix 2. Efficacy Results

Appendix 3. Adverse Events

4 ABBREVIATIONS AND DEFINITION OF TERMS

ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
CGI	Clinical Global Impression
CI	Confidence Interval
COSTART	Coding Symbols and Thesaurus of Adverse Reaction Terms
CRF	Case Report Form
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition
ECG	Electrocardiogram
HAM-D	Hamilton Rating Scale for Depression
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
MADRS	Montgomery-Asberg Depression Rating Scale
MAOI	Monoamine Oxidase Inhibitor
MDD	Major Depressive Disorder
SF-36	Medical Outcomes Study Short-Form Health Survey (36 items)
OC	Observed Cases
QOL	Quality of Life
SASS	Social Adaptation Self-evaluation Scale
SSRI	Selective Serotonin Reuptake Inhibitors
SF	Sexual function questionnaire
T_4	Thyroxine
TCA	Tricyclic Antidepressants
TES	Treatment-Emergent Symptoms
TSH	Thyroid-Stimulating Hormone
UKU	Utvalge för Kliniske Undersökelser – side effect scale

5 ETHICS

5.1 Independent Ethics Committee (IEC)

The protocol and all amendments for this trial were reviewed by Independent Ethics Committees (IEC). The protocol including amendments is stored in the master file at Pharmacia.

Monitoring by Pharmacia and auditing procedures performed prior to, during, and upon completion of this trial have verified that this trial was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

5.2 Patient Information and Consent

Prior to inclusion in the study, each patient was given adequate verbal and written information regarding the objectives and procedures of the study and the possible risks involved. All patients gave signed informed consent prior to inclusion in the study.

6 INTRODUCTION

Major depression is a common disorder, with a lifetime prevalence of 2% to 12% in men and 5% to 26% in women [1]. A diagnosis of depression depends on the presence of significant depressed mood and associated affects, but loss of interest, loss of energy, and impaired social function are also inherent components of major depression [2].

Depression can be treated effectively by a range of antidepressant agents [3]. Approximately 60% to 70% of patients in clinical trials will respond to antidepressants but will fail to go into remission [4], and 25% to 35% will experience full remission after treatment with an effective antidepressant agent [4, 5]. Recent meta-analytic reviews have suggested that the selective serotonin reuptake inhibitors (SSRIs) offer equal efficacy to some of the older antidepressant agents (eg, the tricyclic antidepressants [TCAs]), with the advantage of greater tolerability [6, 7, 8]. Other reviewers have suggested that SSRIs may be of more limited utility in more severely depressed patients and in patients with melancholic symptoms. For example, non-SSRI antidepressants, such as venlafaxine and clomipramine, have been found to be significantly more effective than fluoxetine for the treatment of patients with severe depression [9]. However, the studies that have found approximately equal outcomes on general measures of depression symptoms (eg, the Hamilton Rating Scale for Depression [HAM-D] total scores) do not provide any perspective on whether select agents offer superior treatment on a specific domain of depression symptoms.

Norepinephrine, one of the fundamental neurotransmitters of the brain, has been implicated in the neuronal systems that are important in vigilance, mood, and cognition. Modern neurochemical models of depression focus on the concept that norepinephrine is particularly important in the brain subsystems that underlie energy, interest, and motivation, whereas serotonergic systems have particular importance in modulating impulsivity. Both systems may overlap in modulating mood, sleep, anxiety, and appetite [10]. Current theories on

depression have suggested that there are potential underlying genetic variations in the noradrenergic or serotoninergic systems. The suggestion has been made that roughly a quarter of depressions relate predominantly to noradrenergic problems, a quarter to serotoninergic problems, and that the remaining depressions relate to a mixture of these problems or other issues [4]. This theory may explain why the SSRIs in general are associated with approximately one third full responses (normalization of HAM-D), one third partial responses (improvement but not normalization), and one third non-responses [4]. This conceptualization of depression implies the need for agents that are capable of specifically modifying brain norepinephrine systems. As such, this model is consistent with the original monoamine hypothesis of depression, which was first published by Schildkraut [11].

Reboxetine methanesulphonate (reboxetine mesylate, PNU-155950E, FCE 20124) is a highly selective norepinephrine reuptake inhibitor that has antidepressant activity. The affinity of reboxetine to bind to the norepinephrine reuptake transporter (1.1 nM) is similar to that of desipramine (1.2 nM) and higher than that of imipramine (24 nM), venlafaxine (1060 nM), fluoxetine (1015 nM), sertraline (420 nM), citalopram (40 nM), or citalopram (4070 nM) [12, 13]. At clinically relevant doses, reboxetine does not block serotonin or dopamine reuptake, affect anticholinergic or antihistaminergic receptors, or affect cardiac conduction in the manner underlying the cardiotoxicity of the TCAs.

The currently available agents that affect the norepinephrine system have less receptor specificity than reboxetine and, more importantly, affect other pervasive neurotransmitter systems that produce histaminergic and anticholinergic symptoms, among others. The high level of norepinephrine-uptake selectivity and receptor specificity (ie, the relative lack of activity of reboxetine on other neurotransmitter systems) implies the potential utility of reboxetine as an antidepressant, particularly in depressions that are associated with underlying perturbations of the norepinephrine system and in patients who have symptoms that are associated with reduced energy, interest, and motivation.

The efficacy of reboxetine has been independently demonstrated in multiple short-term, randomized, double-blind, placebo-controlled studies [14-16], and in a long-term, double-blind, placebo-controlled study [17]. The analyses of the trial endpoints from the placebo-controlled studies indicates that a clinically relevant benefit is obtained from a short course (6-8 w.) of treatment with reboxetine.

In addition to improvements in depressive symptoms, treatment-associated improvements in social behavior (measured using the Social Adaptation Self-evaluation Scale (SASS) [18]) were noted in one study. In this study, reboxetine was statistically and clinically superior to both placebo and fluoxetine in improving social functioning. The improvement was evident in both the patients who were and were not in remission from their depressive symptoms and indicated a better quality of remission for social adaptation in the reboxetine-treated patients.

The most frequently reported adverse events associated with the administration of reboxetine, as determined from combined safety data from controlled and uncontrolled studies in which 2140 patients have been treated with reboxetine, are dry mouth, constipation, nausea, insomnia, dizziness, headache, and sweating. However, these events were usually mild to moderate in severity, and only a small proportion of patients discontinued treatment with reboxetine for these reasons.

7 OBJECTIVES

7.1 Primary Objective

The Primary objective was to assess efficacy and tolerability of reboxetine in comparison with citalopram in patients suffering from Major Depressive Disorder (MDD) as determined by the HAM-D rating scale.

7.1.1 Primary Endpoint

The primary efficacy measure was the absolute change from baseline to week 24 of the 21-item HAM-D total score.

7.2 Secondary Objective

To assess efficacy of reboxetine in comparison with citalopram in patients suffering from MDD as determined by the Montgomery-Asberg Depression Rating Scale (MADRS), Clinical Global Impression (CGI), and Social Adaption Self-evaluation Scale (SASS) scales.

7.2.1 Secondary Endpoints

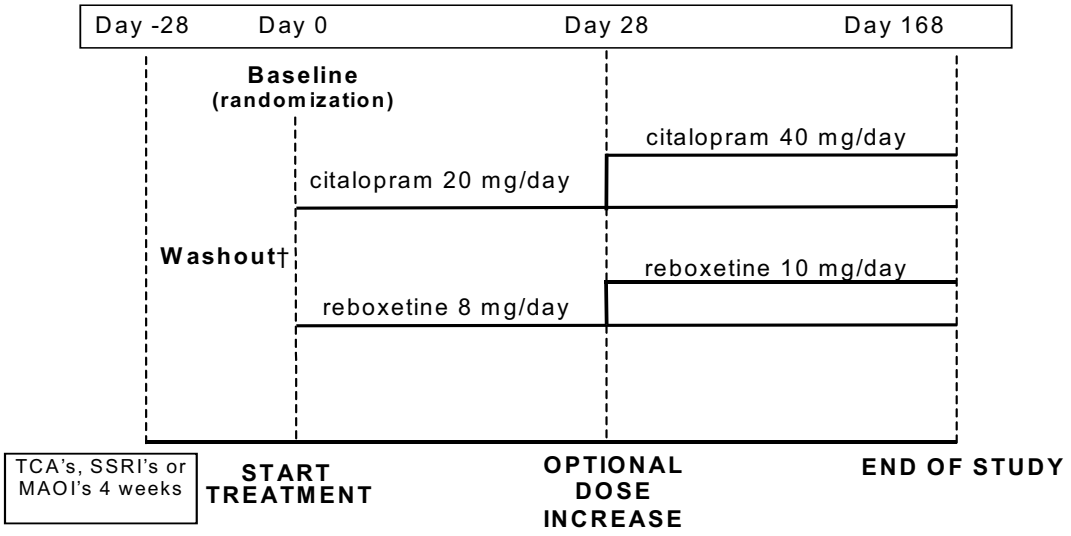
The secondary efficacy measures are mean change from baseline in the MADRS and CGI, total score, response/remission rates, and time to response/remission. A decrease of at least 50% in the HAM-D total score versus baseline was considered the index of response whereas a HAM-D total score of 10 or less was considered index of remission. Additional secondary efficacy measures included measures of social functioning, using the SASS, and sexual function, using the Sexual Function Scale. For details on these variables, see section 8.3 .

8 METHODS

8.1 Overall Study Design and Plan

This phase IV study was carried out according to a randomised, double-blind, parallel groups, fixed/flexible-dose design, reboxetine vs citalopram. The study was organized on a multicenter, multinational basis (Scandinavia). Adult patients were selected from the population attending out-patient or day-hospital clinics. After randomization the experimental treatment was continued for 24 weeks. Study visits were conducted at baseline, week 2, 4, 6, 12, 18 and week 24, or after drop-out. Efficacy and safety measures were assessed at every visit. At the end of the 24 weeks double blind treatment period the patients was, by the investigator, considered to need further treatment or not. For the patients judged to need further treatment the investigator was recommended to prescribe a marketed antidepressant of their choice. For the patients not considered in need of further treatment, a 2 week blinded tail off was recommended. The study design is presented in Figure 1.

Figure 1. Study Design and Timeline



8.1.1 Discussion of Study Design

The double-blind, randomized, parallel-group design that was used in this study is generally recognized as one that provides an unbiased assessment of the efficacy and safety of an experimental drug. The active comparator, citalopram, was chosen because it is one of the most commonly prescribed SSRIs and because its' efficacy and safety have been proven and documented in several placebo- and active-controlled trials.

HAM-D was chosen as the primary efficacy measure in this study because its used in a wide variety of populations, and has proven its validity and reliability. This rating scale has, therefore, become accepted internationally as a standard measure of the severity of depression in psychiatric research. The MADRS, CGI, and SASS scales were chosen as the secondary efficacy measure in this study. The MADRS, a newer rating scale than the HAM-D, has also been used successfully to assess the severity of depression, and has been shown to be sensitive to changes in patient symptoms. The CGI has been routinely used as an outcome measure in therapeutic trials. The SASS is an easy-to-handle self-rating scale that provides a means of collecting patient perception of his/her level of social motivation and functioning.

8.1.2 Study Population

8.1.2.1 Inclusion Criteria

To be included in the study, patients must have met all of the following criteria:

- Diagnosis of MDD without psychotic features, as defined by DSM-IV.
- Male or female, of any race, between the ages of 18 and 70 years (local amendement in Denmark 16-71 years).
- If female, must have been postmenopausal or must have met all of the following criteria:
    - agreed to avoid pregnancy during the study
    - negative serum pregnancy test at screen
    - used an accepted means of birth control (as determined by the investigator), such as oral contraceptive, implantable or injectable contraceptive, intrauterine device, or barrier method, or have been surgically sterilized
- Total score of ≥22 on the 21-Item HAM-D at screen and confirmed at baseline. If the time period between screening and baseline was less than 3 days, the HAM-D score at screening could be used. Voluntary consent to participate in the study documented in a written Patient Informed Consent Form that was signed prior to the start of any study procedures at the screening visit.

8.1.2.2 Exclusion Criteria

Patients were excluded from the study for any of the following reasons:

- DSM-IV diagnosis of the following concomitant psychiatric disorders: MDD with psychotic features, dysthymic or cyclothymic disorder, bipolar I or bipolar II disorders, substance-related disorders, schizophrenia, or other psychotic disorders.
- A lack of response to at least two previous course of antidepressants given as full doses for more than one month.
- History of MDD associated with endocrine disorders: hypo- or hyperthyroidism tested by thyroid-stimulating hormone and thyroxine, adrenal insufficiency, or Cushing's syndrome, etc.

- Positive serum pregnancy test for females of childbearing potential.
- Breast-feeding female patients.
- Participation in a clinical study with an investigational compound in the 4 weeks preceding the study.
- Presence of gastrointestinal, liver, or kidney disease or other conditions known to interfere with the absorption, distribution, metabolism, and excretion of drugs.
- History of seizures or brain injury; current evidence of clinically important hematopoietic, respiratory, or cardiovascular diseases; current evidence of urinary retention or glaucoma.
- Clinically significant illness in the 4 weeks preceding the study that might have interfered with the conduct of the trial.
- Clinically relevant abnormal findings in the physical examination, laboratory tests, or ECG at admission.
- Treatment with electroconvulsive therapy in the 6 months preceding the study.
- Major risk of suicide as assessed by the investigator, a score of ≥3 on Item 3 of the HAM-D at screen or baseline, or a history of suicide attempt during the current depressive episode.
- History of hypersensitivity to reboxetine or citalopram.
- Use of the following medications, which are known to inhibit major drug-metabolizing enzymes other than cytochrome p450-2D6: azole antifungals, macrolide antibiotics (such as erythromycin), or fluvoxamine.
- Use of oral anticoagulants (such as warfarin) that are known to inhibit vitamin K-dependent coagulation factors.
- Use of concomitant psychotropic medications other than the protocol-specified sedatives/hypnotics, which could be taken on an as-needed basis for sleep.
- Inability of the patient to comply with the conditions of the study based on the investigator's assessment.
- History of drug or alcohol abuse.

8.1.2.3 Removal of Patients From Therapy or Assessment

A patient should be withdrawn from the study treatment if, in the opinion of the Investigator, it was medically necessary or if it was the wish of the patient. In case of treatment discontinuation, the reasons for the withdrawal should be clearly described and the patient should, whenever possible, irrespective of the reason for withdrawal, be examined as soon as possible. Termination of study medication prior to study completion was considered in cases of adverse events, pregnancy, increased risk of suicide, clinical deterioration, or mania. The reasons for the withdrawal of study medication were noted. Relevant samples (lab tests and any diagnostic procedure necessary to define the event leading to withdrawal) were obtained

and all relevant assessments were completed, preferably according to the schedule for final assessment. The CRFs were completed and collected by the Pharmacia Monitor.

8.2 Treatments

8.2.1 Trial Products

Capsules containing reboxetine 8 mg (4 mg PresTabs BID) or 10 mg (4 mg + 2 mg PresTabs, 6 mg morning and 4 mg evening dose), citalopram 20 mg (20 mg tabs) or 40 mg (40 mg tabs) plus placebo, was supplied by Pharmacia. Drug supplies were stored at room temperature. All drug supplies was handled under the direct responsibility of the Investigator and held by the Hospital Pharmacy or by the Investigator himself. Before treatment was started, all patients were checked for eligibility according to the inclusion/exclusion criteria and a signed written informed consent was obtained from each patient. During the study the only psychoactive medications allowed were: temazepam, lorazepam, oxazepam, zoplicone and zolpidem as sleep inducer on p.r.n. basis.

8.2.2 Identity of Investigational Products

For each patient packages labeled with trial, patient and week number was prepared. The package for the first 4 weeks of treatment contained 2 bottles, 1 for the morning dose (marked level 1) and 1 for the evening dose. Following packages contained 3 bottles, 2 for the morning dose (marked level 1 & 2) and one for the evening dose. The investigator removed either level 1 or level 2 morning bottle depending on wether the patient should recieve the increased morning dosage (level 2) or continue with the same dosage as week 1-4 (level 1). Each bottle contained 35 capsules including 7 additional capsules. Information about the study medications is summarized in Table 1.

Table 1. Study Medications: Capsule Strength, Manufacturers, and Batch Numbers

Study Medication	Capsule Strength	Manufacturer
Reboxetine	2mg (one 2-mg PresTab)	Pharmacia
Reboxetine	4mg (one 4-mg PresTab)	Pharmacia
Reboxetine	6mg (one 2-mg PresTab and one 4-mg PresTab)	Pharmacia
Citalopram	20mg (one 20-mg PresTab)	Lundbeck *
Citalopram	40mg (one 40-mg PresTab)	Lundbeck *
Placebo	Not applicable	Pharmacia

* Cipramil tablets, manufactured by H. Lundbeck A/S, were inserted into gelatin capsules by Pharmacia.

During week 0 to 4, each patient was instructed take one capsule in the AM and one capsule in the PM. Treatment should be administered in the morning and in the evening at approximately a fixed time. From week 0 to 4, patients randomized to reboxetine recieved bottles in which each dose (morning and evening) consisted of a capsule containing 4 mg reboxetine as the free base, i.e. a dose of reboxetine 4 mg BID. From weeks 0-4, patients randomized to citalopram received bottles in which the morning dose consisted of a capsule containing 20 mg citalopram and the evening dose was a placebo capsule, i.e. a dose of citalopram 20mg QAM and one placebo QPM.

At the week 4 evaluation, the investigator was allowed to increase the daily dose if it was judged that the patient would benefit in terms of response and would adequately tolerate the increased dose. The dose increase was accomplished by using level 2 morning bottles. For patients randomized to reboxetine, this bottle contained capsules containing 6 mg reboxetine as the free base to be taken each morning. The dose for these patients from week 5-24 was therefore reboxetine 6 mg QAM and 4 mg QPM (reboxetine 10 mg/day total). For patients randomized to citalopram, this bottle contained capsules containing 40 mg citalopram to be taken each morning. The evening dose wasl still a placebo capsule. The dose for these patients from week 5-24 was citalopram 40 mg/day total. Patients who received escalated dose at week 4 continued with the higher dose until completion of treatment on week 24 unless untolerable side effects appeard, in which case the regimen used in week 0-4 was restarted.

8.2.3 Method of Assigning Patients to a Treatment Group

Pharmacia prepared a randomization list for patient assignment to 1 of the 2 treatment groups. Study medication for each treatment group was prepared on this basis by Pharmacia and was labeled with the corresponding patient number. At the baseline visit, the investigator assigned each patient to a treatment group based on the patient's temporal entry into the study (ie, by assigning the lowest patient number available). A list of patient numbers and medication assignments was provided only after the data for the study had been analyzed. The study blind was broken based on the status of the database when all patients had completed the 24-week treatment period.

8.2.4 Selection of Doses and Timing of Dose

The 8- to 10-mg/day doses of reboxetine that were administered in this study were chosen based on the results of previously conducted phase II and phase III studies in which these doses were shown to provide maximal response rates with the most acceptable adverse-event profile.

The starting dose of citalopram that was administered in this study (20 mg/day) has been shown to be the minimally effective and optimal dose for most patients. The optional dose increase to 40 mg/day of citalopram is consistent with the current therapy recommendations at Scandinavian physiatric clinics.

Throughout the study period, patients in each of the treatment groups took one capsule in the morning and one capsule in the late afternoon, at an approximately fixed time (eg, between 8 and 9 AM and between 5 and 6 PM).

8.2.5 Blinding

Patients were randomized to a treatment in a double-blind fashion in order to minimize potential bias in the evaluation of clinical response and safety. The randomized medication consisted of identically appearing capsules containing reboxetine or citalopram with placebo. The capsules were provided in clinical supply packages that were labeled (in the appropriate language) with the protocol number, patient number, treatment period, dose level (I or II), dosing directions, and storage conditions.

Investigators were given sealed drug-disclosure sheets containing information that revealed each patient's treatment assignment. These sheets were opened only in case of emergency, when knowledge of the treatment was necessary for proper management of the patient. If the drug-disclosure sheet was opened, the reason and the date were recorded on the serious adverse event report form, which was signed by the investigator. The investigator immediately (within 24 hours) informed the study monitor and reported a full description of the reason for opening the code on the Adverse Event Form of the CRF. When the treatment code was opened, the patient was to be withdrawn from the study.

The sealed disclosure sheets were returned to Pharmacia at the end of the study.

8.2.6 Prior and Concomitant Therapy

During the study the only psychoactive medications allowed were: temazepam, lorazepam, oxazepam, zoplicone and zolpidem as sleep inducer on p.r.n. basis. The administration of other psychotropic drugs was considered to be a protocol violation leading to the exclusion of the patient from the study. Use of St. John's Wort was not allowed during the study.

Other therapy that was considered necessary for the patient's welfare was permitted at the investigator's discretion. All such therapy was recorded on the Non-Investigational Medication CRF.

No other investigational drug or drug mentioned in the exclusion criteria was permitted concomitantly with the study medication, and patients were not allowed to participate concurrently in any other clinical study. Over-the-counter medications were allowed as needed for symptomatic treatment; these were recorded along with other medications on the Non-Investigational Medication CRF.

8.2.7 Treatment Compliance

The investigator maintained a record of the study medications that were received from the sponsor, those that were dispensed, and those that were returned. Discrepancies between the number of capsules dispensed and returned were recorded.

Acceptable patient compliance during or following treatment was defined as an overall drug intake of at least 80% of the prescribed amount. Treatment compliance was monitored by the investigators and was recorded on the appropriate CRF at each visit.

8.2.8 Continuation of Treatment

For the patients judged to need further treatment after week 24, the investigator was

recommended to prescribe a suitable antidepressant of their choice. For the patients not considered in need of further treatment, a 2 week blinded tail off was recommended.

8.2.9 Study Schedule

The schedule of study activities is summarized in Table 2.

Table 2. **Study activities**

Visit	**Screen**	**Baseline**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
Week	**-1**	**0**	**1**	**2**	**4**	**6**	**12**	**18**	**24**	**26**	**Drop**
	≤ 7 days	Day 1	± 2 days	± 2 days	± 2 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	
Informed consent	✓										
Incl/ Exclusion criteria	✓	✓									
Diagnosis: DSM IV	✓								✓a		
Medical history	✓										
Physical examination	✓						✓		✓		✓
Laboratory (not more than 3 months old)	✓				✓		✓b		✓		✓
Pregnancy test	✓								✓c		✓
Pulse and blood pressure	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
21-item HAM-D	✓	✓d		✓	✓	✓	✓	✓	✓		✓
MADRS		✓		✓		✓	✓		✓		✓
CGI	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
SASS		✓		✓		✓	✓		✓		✓
SF		✓		✓		✓		✓	✓		✓
DIP-Q		✓							✓		✓
GAF		✓		✓	✓	✓	✓	✓	✓		✓
Health Economics	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
Drug account					✓		✓	✓	✓	✓	✓
Dispensing Med.		✓			✓		✓	✓	✓e		
Adverse Events (spontaneous + UKU)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

a) Depression chapter only
b) Only pharmacokinetic blood sampling (Sweden)
c) If end of treatment else than at 24-26 weeks
d) Only if baseline visit is performed > 5 days from screen visit
e) For those patients who tailed off after week 24.

*) CGI - severity of illness and/or improvement

**) See section 8.3

8.3 Efficacy

8.3.1 Efficacy Variables

Efficacy was evaluated at every visit except at week 1 (weeks 0, 2, 4, 6, 12, 18, and 24) or at the drop-out visit. The efficacy measures used are summarized in Table 3.

Table 3. Efficacy Measures

Domain	Assessment Instrument	Endpoint	Rater
Depression	21-Item HAM-D	Primary	Clinician
	MADRS	Secondary	Clinician
	CGI	Secondary	Clinician
Social Function	SASS	Secondary	Patient
Sexual Function	SF	Secondary	Patient

Abbreviations: HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale, CGI = Clinical Global Impression, SASS = Social Adaptation Self-evaluation Scale, SF = Sexual Function Scale

8.3.1.1 Description of Efficacy Scales

All clinical efficacy assessments were to be done by the investigator/co-investigator or personnel suitably trained and delegated by the primary investigator. All psychiatric evaluations and ratings were to be carried out by the same observer for a given patient, preferably in the same setting and at the same time of day.

Hamilton Depression Rating Scale

The 17-, 21-, and 28-Item HAM-D [19] are observer-rated scales that are based on both a clinical interview and on observations of behavior made by an experienced clinician. This scale is well standardized and is intended to assess the state of the patient's condition at the time of the interview and over the preceeding few days. The individual items on the HAM-D 21-item HAM-D of ≤10 are often used as the definition of disease remission. Response to study medication is defined as a decrease of ≥50% from baseline in the HAM-D total score at the postbaseline assessment.

The response and remission rates were calculated for the whole population as well as for the depression types: mild, moderate or severe melancholic and non-melancholic depression respectively. The depression types were defined by the use of the sum of the following HAM-D 21 items at baseline: 2, 6, 8, 9, 12 and 18a, see Table 4. The quartiles for the total score of these items were used as cut-off for dividing the patients into the four depression types.

Montgomery-Asberg Depression Rating Scale

The MADRS , which is based on a clinical interview, has been shown to satisfactorily distinguish between 5 grades of depression [20, 21]. In the MADRS, categories of degree are precisely described, items are restricted to representing only those symptoms that are considered to be the core symptoms of depressive syndromes, and items representing somatic complaints have been reduced. The MADRS consists of 10 items, each of which is scored on a 7-point scale on which 0 corresponds to the absence of the symptom and 6 corresponds to the most extreme form of the symptom. The MADRS total score ranges from 0 to 60. Remission is defined as a MADRS total score of ≤12. Response to study medication is defined as a decrease of ≥50% from baseline in the MADRS total score at the postbaseline assessment.

Clinical Global Impression

The CGI [22] consists of the following 2 parts: Severity of Illness, and Global Improvement. A mean decrease from baseline on the CGI Severity of Illness score represents patient improvement. The Severity of Illness and Global Improvement parts are 7-point measures, with lower scores indicating better health. The questions from the Global Improvement index refer to changes since the beginning of the study, as evaluated at each postbaseline visit, and are not asked at baseline. Lower scores on the CGI Global Improvement index indicate patient improvement; a responder is defined as a patient who has a score of ≤ 2 (corresponding to “very much improved” or “much improved”).

The Social Adaptation Self-evaluation Scale

The SASS is a 21-question self-evaluation questionnaire that explores the domains of work and leisure, relationships, and patient perception of his/her ability to manage the environment. The scale was validated using data from 4000 individuals in a general population survey and data from 549 depressed patients who were enrolled in clinical studies that compared reboxetine with placebo and/or fluoxetine [18]. Each item of SASS is scored on a scale of 0 to 3, with a higher score indicating better social functioning. A total score in the range of 35 to 52 points is considered to be normal (ie, this range was observed in 80% of the general population). The SASS represents a useful tool for the evaluation of social functioning in depression because it is relatively simple to use and because it may help to differentiate the effects of different classes of antidepressants (eg, serotonergic agents regulating mood, noradrenergic agents sustaining drive) in a way that syndromic clinical rating scales are unable to do.

Sexual Function questionnaire

The Sexual Function (SF) questionnaire is a validated self administered questionnaire developed in Sweden [23], based on the English Sexual Functioning Questionnaire (SFQ) [24]. SF measures the change in sexual function over time, i.e. from baseline to 2, 6, 12 and 24 weeks. Patients with earlier sexual problems (unrelated to the depression disease) can be detected and are possible to exclude from the analysis. Both total scores and changes from baseline can be used in the statistical analysis.

Other diagnostic parameters and analysis

Registration of personality characteristics were carried out using DIP-Q (DSM-IV and ICD-

10 Personality Questionnaire) at baseline and at the end of the study. DIP-Q is an 140-items self-report questionnaire for assessment of all 10 DSM-IV and all eight ICD-10 personality disorders. The DIP-Q items consist of brief statements reflecting the main aspects of the corresponding criteria and the respondent is asked to score the statement as true or false. The questionnaire has been validated in several studies and in several clinical samples [25, 26].

Aspects of the general criteria for personality disorders are also evaluated. The self-report version of the global assessment of functioning (GAF) scale is included in the DIP-Q. The GAF-self scale is based on the original 0 - 100 scale (axis V in the DSM-IV) and has been developed and evaluated by Bodlund et al [27].

The use of DIP-Q enables analysis of possible correlations between efficacy outcome and personality characteristics. Expert evaluation of the GAF (axis V) were carried out, besides at baseline and endpoint, also at week 2, 4, 6, 12 and 18, which makes it possible to analyse also the GAF as an efficacy measure and correlate it to the SASS, CGI, HAM-D etc. DIP-Q and GAF results will be reported separately.

Gender specific analysis were performed .To analyse the possible correlation between the type of depression and outcome in the therapeutic effect of the two treatments, a special "melancholia index" was created in cooperation between Pharmacia and the investigators.. The grade of melancholia was estimated based on scores in the HAM-D items 2, 6, 8, 9, 12 and 18A respectively. These items were selected as the most corresponding to the DSM IV criteria of melancholia, Table 4. The population was divided into two subgroups where the median score of the "melancholia index" was cut off. Differences in therapeutic effect (response and remission) between the two treatments were analysed.

Table 4. **"Melancholia index"**

Symptoms/signs (DSM IV)	HAM-D item
Feelings of guilt	**2**
Early awakening	**6**
Psychmotoric retardation	**8**
Agitation	**9**
Loss of appetite	**12**
Mood worse in morning	**18A**

8.3.1.2 Health economics

The primary objective of the health economic analysis was to estimate the medical and non-medical resource utilization in the reboxetine and citalopram patient groups over a 6 months period. A second objective was to estimate the relative cost-effectiveness of reboxetine vs

citalopram in the treatment of major depressive disorder by comparing both costs and outcome as measured by the Hamilton Depression Rating Scale.
Health economic endpoints were:

- Cost consequences (resource utilization) in both treatment groups over a 6 months treatment period.

- Cost-effectiveness of reboxetine compared to citalopram, i.e., difference in total resource utilization (cost) in relation to difference in treatment outcome.

The health economic analysis were made from two perspectives:

a) The societal perspective, where all costs regardless of who incur them were be considered.
b) The payer/provider perspective, where costs were estimated from the viewpoint of the health care system, i.e., costs incurred by the health care providers.

Cost analysis
The aim of the cost analysis was to measure the resource utilization in both treatment groups over a 6 months period. Both direct costs (medical resource utilization) and indirect costs (cost due to lost productivity) were analyzed. Cost was expressed as the monetary value of the utilization of the following resources:

- number of visits to General Practitioners and to other physician specialists (unscheduled and scheduled)
- number of nurse visits (or visits to other health care personnel categories)
- reboxetine and citalopram medication
- concomitant medication
- number and type of laboratory tests
- (inpatient) hospitalizations
- number of days of lost working time due to illness

Data on medical and non-medical resource utilization were extracted from the case report forms. Resource utilization data were recorded for all patients included in the clinical trial at each visit. National cost averages or tariffs will be used as basis for the determination of unit costs for each resource category.

Cost-Effectiveness analysis
The cost-effectiveness analysis estimated the cost per patient with a clinically significant response to treatment after a 6 months period. Clinically significant response was defined as patients achieving a 50% reduction in the HAM-D 21 item total score compared to baseline.

Incremental analysis based on the societal perspective was performed using the following

formula:

$$\frac{\left(\text{Cost}D^{Re} + \text{Cost}O^{Re} + \text{Cost}I^{Re}\right) - \left(\text{Cost}D^{Ci} + \text{Cost}O^{Ci} + \text{Cost}I^{Ci}\right)}{\#\text{Response}^{Re} - \#\text{Response}^{Ci}}$$

where D = drug costs (incl. concomitant medication)
O = cost of other medical resources
I = indirect costs (productivity costs)
Re = reboxetine group
Ci = citalopram group
# Response = number of patients with ≥ 50% reduction in HAM-D 21 item total score
For the analysis using the health care system perspective, the nominator of the formula contained only direct costs. In both the cost analysis and the cost-effectiveness analysis, the estimations was based on the intention-to-treat data set. No discounting was used since all cost and outcome consequences occured within a one-year period. Mean values and 95% confidence intervals for the cost difference and the cost-effectiveness ratio was estimated.

8.4 Safety and quality assurance

8.4.1 Safety Assessments

The following safety variables were assessed in this study:

- Standard medical history, including physiatric history, obtained at screen.
- Standard physical examination at screen.
- Blood pressure and pulse measured at screen and each visit in the supine position (after 5 minutes supine).
- Adverse events recorded at each visit, both spontaneously reported and according to the UKU scale [29].
- Laboratory analyses

The following laboratory samples were analyzed at screening, week 4, 12 and at the end of treatment: blood count, Na, K, Ca, S-creatinine, S-ASAT, S-ALAT, and uric acid. U-glucose and urine pregnancy test (for women of child-bearing potential) was performed at screening.

To investigate possible concentration-effect and concentration-side effect relationships, blood samples for pharmacokinetic (PK) analyses of RBX (racemate) was collected at week 4, 12 and 24 (or at drop out) from all Swedish patients included in the study. The full blood samples were centrifuged on the same day to recieve serum samples. These samples were then stored at -20°C. Analyses of the serum concentration of reboxetine and reboxetine

enantiomers were to be performed at Dept of Clinical Chemistry, University Hospital, Linköping, Sweden, after the study completion. Details from the PK analysis will be reported separately.

8.4.1.1 Adverse Events

An adverse event was defined as any untoward medical event that occurred during the protocol-specified adverse event reporting period (from the first dose of investigational medication until 1 week after the final clinic visit) regardless of whether it was considered to be related to study medication. In addition, any known untoward event that occurred subsequent to the adverse event reporting period and that the investigator assessed as possibly related to the investigational medication was also considered to be an adverse event.

Adverse events included all suspected adverse medication reactions; all reactions from medication overdose, abuse, withdrawal, sensitivity, or toxicity; apparently unrelated illnesses, including the worsening of a preexisting illness (except for worsening of depressed mood); any injury or accident; and any abnormality in physical examination or laboratory test results that required clinical intervention or further investigation (beyond ordering a repeat confirmatory test). If a medical condition was known to have caused the injury or accident (eg. a fall secondary to dizziness), then the medical condition (dizziness) and the accident (fall) were reported as 2 separate adverse events. The outcome of the accident (eg. hip fracture secondary to the fall) was recorded in the comments section of the CRF. Laboratory abnormalities that were associated with a clinical event (eg. elevated liver enzymes in a patient with jaundice) were described in the comments section of the CRF, rather than listed as a separate adverse event.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, were not reported as adverse events. However, the medical condition for which the procedure was performed was reported if it met the definition of an adverse event (eg, an acute appendicitis that began during the adverse event reporting period would have been reported as an adverse event; the resulting appendectomy would have been noted in the comments section of the CRF).

Except for worsening of depressed mood (which would be reflected in a change in the HAM-D Item 1 score), an increase in the intensity of other symptoms of depression (eg, sleep difficulties, somatic symptoms, genital symptoms, weight change, anxiety, other psychiatric symptoms) was to be considered an adverse event if the intensity of the event increased during the treatment period.

Eliciting Adverse Event Information

Investigators reported all directly observed adverse events and all adverse events that were spontaneously reported by the patients and not present at baseline. In addition, each patient was questioned about adverse events at each clinic visit, firstly in an open-ended manner, and secondly according to a specific check-list, the UKU scale, where different symptoms were listed [28].

Adverse Events Reporting

The adverse event reporting period began with the administration of the first dose of study medication (at the baseline visit) and ended at the final clinic visit. An adverse event that occurred during the protocol-specified adverse event reporting period was recorded, regardless of whether it was considered to be related to the study medication. A disorder that was present before the adverse event reporting period started and that was noted on the pretreatment medical history/physical examination form was not reported as an adverse event unless the condition worsened or episodes increased in frequency during the adverse event reporting period. Any known untoward event that occurred subsequent to the adverse event reporting period, whether the investigator assessed it as possibly related to the study medication or not, was considered to be an adverse event.

If a serious adverse event occurred, the Pharmacia Monitor should be notified, using the designated form (clinical trial adverse event CRF), within 24 hours of awareness of the event by the Investigator. The initial report was to be followed by submission of more detailed adverse event information within 5 working days of the event. Unexpected, serious adverse events were to be reported immediately to the responsible Medical Product Agency and Institutional Review Board/Independent Ethics Committee.

Non-serious adverse events should be reported on the adverse event CRFs, which should be submitted to Pharmacia as specified in the adverse event report submission procedure for this protocol.

Assessment of Gravity and Intensity

Each adverse event was classified by the investigator as serious or non-serious. A serious adverse event was one that was fatal or life-threatening (ie, resulted in immediate risk of death), required or prolonged hospitalization, resulted in persistent or significant disability/incapacity, or was a congenital anomaly. Any other important adverse event that did not meet the preceding criteria was classified as serious if, based upon appropriate medical judgment, the event resulted in permanent impairment of function or permanent damage to a body structure or if medical or surgical intervention was required to prevent permanent impairment or damage. Serious adverse events also included any other adverse event that the investigator or company judged to be serious or that was defined as serious by the regulatory agency in the country in which the adverse event occurred.

Investigators characterized the intensity of adverse events as mild (did not interfere with subject's usual function), moderate (interfered to some extent with subject's usual function), or severe (interfered significantly with subject's usual function). The assessment of intensity was made independently of the assessment of gravity. It should be noted that severity is a measure of intensity, whereas seriousness is a measure of gravity. (A severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed above.)

Assessment of Drug-Relatedness

Investigators assessed the possible relationship between the adverse event and the study

medication as well as any concomitant medications.

Follow-up of Unresolved Events

All adverse events were followed until they resolved or until the patient's participation in the study ended (ie, until a final report was completed for that patient). In addition, all serious adverse events and those non-serious events that were assessed by the investigator as possibly related to the study medication were followed after the patient's participation in the study was over, until the events resolved or until the investigator assessed them as "chronic" or "stable."

Exposure In Utero

If a patient became, or was found to be, pregnant while receiving or within 30 days of discontinuing study medication, then the investigator submitted an adverse event CRF that included the anticipated date of birth or pregnancy termination. The patient was followed by the investigator until the completion of the pregnancy. If the pregnancy ended for any reason prior to the anticipated date provided, the investigator was to notify the monitor. The following pregnancy outcomes were to be reported as serious adverse events: spontaneous abortion (including miscarriage and missed abortion), stillbirth, neonatal death within 1 month of birth, infant death that occurred after 1 month of birth and that the investigator assessed as possibly related to the in utero exposure, or congenital anomaly (including that in an aborted fetus). In the case of a live birth, the “normality” of the newborn was assessed at the time of birth (ie, there was no required minimum follow-up of a presumably normal infant). The “normality” of an aborted fetus was assessed by gross visual inspection unless pre-abortion laboratory findings were suggestive of a congenital anomaly.

8.5 Quality control and quality assurance

The following procedures were implemented to ensure the quality of data that were collected:

- An investigator’s meeting was held to familiarize the investigators with the protocol and with the assessment instruments. HAM-D inter-rating training was carried out.
- A reference manual was given to each investigator.
- Data were collected on standard CRFs that were provided to each investigator by the sponsor.
- Monitoring visits were made periodically during the study to ensure that all aspects of the protocol were followed.
- Source documents were reviewed to verify their agreement with the data on the patient CRFs.
- All safety laboratory measurements were conducted by laboratories certified by International Standard (ISO) became Quest Diagnostics, and were transmitted electronically to P&U for analysis.

- The International Conference on Harmonization of Good Clinical Practice Guidelines and Practices and all applicable laws in the country in which the study was conducted were followed.
- Pharmacia's Standard Operating Procedures were followed in the conduct and analysis of the study.

Instructions for completion and submission of these forms were included in the Investigators File. All information relevant to subject safety or study endpoints had to be recorded.

9 STATISTICAL AND ANALYTICAL METHODS

9.1 Analysis of data and study population

The following case report forms contained data that would permit pre-study comparisons of patients randomized into the two treatment groups: a/ medical history, b/ physical examination, c/ history of mental disorder, and d/ baseline efficacy forms. For the continuous variables (ie, HAM-D total, MADRS and SASS total), testing for difference between 2 treatment groups was performed using a 2-way analysis of variance (ANOVA) model that included treatment, investigator, age, and baseline terms. A group difference of 2.5 or more in HAM-D total score was assessed to be clinically significant.

Treatment-by-center interaction was explored and included if it contributed significantly to the model. The response variables were to be the change from baseline scores at each visit. Categorical data (ie, response and remission) were to be analysed by Cochran-Mantel-Haenszel (CMH) test. In addition to p-values, 95% confidence intervals for the difference between 2 treatment groups would also be computed for HAM-D total mean change from baseline, SASS total mean change from baseline, response rate, and remission rate.

Two types of analyses should be performed for the primary variable i.e. HAM-D 21 total score: “last observation carried forward” (LOCF) and “observed cases” (OC). The LOCF analysis uses the last valid assessment as an estimate for all subsequent missing values. The OC analysis does not replace missing data. The LOCF was to be regarded as the primary analysis and the OC was to be secondary. Table 5 describes the populations that the statistical analyses were based on.

Table 5. **Study population**

	Total	Reboxetine	Citalopram
Randomised patients	359	183	176
Randomised patients who received study drug	357	181	176
Completed patients	214	92	122
Withdrawn patients	145	91	54
Patients included in FAS	350	177	173
Patients included in FAS analysis of HAM-D 21 (OC)	216	93	123
Patients included in FAS analysis of HAM-D 21 (LOCF)	320	156	164
Patients included in the safety analysis	357	181	176

The analysis of HAM-D 21 was conducted for the total population and for each of the following groups:
1/ HAM-D 21 severely ill patients (patients scored > 32 on the HAM-D 21 total score at baseline), 2/ HAM-D 21 non-severe patients (patients that were not HAM-D 21 severely ill),

3/ Males/Females, 4/ CGI severely ill patients (patients scored 5 to 7 on the CGI severity of illness scale at baseline), 5/ CGI non-severe patients (patients that were not CGI severely ill).

9.2 Demographic Characteristics

The treatment groups were well balanced with respect to demographic data. The mean age for the reboxetine group was 42.8 years (range 19-71) and the citalopram group had a mean age of 41.5 years (range 16-65). Thus, 2 patients with age outside the stipulated age range were included (local amendment), see table 6.

Table 6. **Description of age**.

Treatment		n	Mean	Median	Std	Min	Max
Age (years)	**Reboxetine**	177	42.8	43.0	13.3	19	71
	Citalopram	173	41.5	42.0	12.0	16	65

55 subjects (31%) in the reboxetine group and 70 subjects (40%) in the citalopram group were males. All patients except three were caucasian. There was one patient with oriental origin and one with hispanic origin in the reboxetine group. One patient in the citalopram group had asian origin. Two patients were only included in the safety analysis. They were both caucasian females aged 24 and 52 years. See Tables 7-8.

Table 7. **Ethnic origin distribution**

Ethnic origin	Treatment			
	Reboxetine		Citaloprom	
	n	%	n	%
Caucasian	175	98.9	172	99.4
Asian	0	0	1	0.6
Oriental	1	0.6	0	0
Hispanic	1	0.6	0	0
Total	177	100.0	173	100.0

Table 7. **Gender distribution.**

Gender	Treatment			
	Reboxetine		Citalopram	
	n	%	n	%
Male	55	31.1	70	40.5
Female	122	68.9	103	59.5
Total	177	100.0	173	100.0

On physical examination, no statistically significant difference between treatment groups was noted. No statistically significant differences in the medical history findings were noted among the treatment groups, and no statistically significant differences were noted among the treatment groups in the severity of depression at baseline in randomized patients, as judged by the mean total scores for the HAM-D, MADRS or CGI (severity of illness).

9.2.1 Study completion

91 of the 181 patients in the reboxetine group were withdrawn from the study before the 24 week visit. The corresponding figure for the citalopram group was 54 of 176. The higher drop-out rate in reboxetine means that the treatment groups were unbalanced with respect to number of patients at the end of the study. 214 patients (93 reboxetine treated and 123 citalopram treated) completed the 24 weeks visit. Table 9 below shows the distribution of reason for withdrawal before study completion.

Table 9. **Reasons for withdrawal (number of patients).**

Reason for withdrawal	Treatment	
	Reboxetine	Citalopram
Adverse Event	36	9
Other medical event	1	0
Unsatisfactory efficacy	16	6
Missing visit	10	14
Protocol violation	3	4
Patient's own decision	22	21
Other non-medical event	3	0
Total	91	54

9.2.2 Dose levels

The last known dose level in the study is summarised in the table below. The proportion of patients on low/high dose level at study end was similar in the treatment groups, Table 10. Average daily dose of reboxetine was 8.7 mg, and of citalopram 30 mg.

Table 10. **Last known dose levels in the two treatment groups.**

Treatment	Dose level	n	%
Reboxetine	**8 mg/day**	115	63.5
	10 mg/day	66	36.5
	Total	181	100.0
Citalopram	**20 mg/day**	106	60.2
	40 mg/day	70	39.8
	Total	176	100.0

10 RESULTS

10.1 Efficacy Endpoints

10.1.1 HAM-D, MADRS and CGI

The primary efficacy endpoint was the change in HAM-D 21 from baseline to week 24. The OC analysis showed no statistically significant difference between the treatments for this endpoint. The mean change from baseline to week 24 was –21.4 for reboxetine and –22.1 for citalopram. Mean scores at the different time points are shown in Table 11, and in Appendix 1, Figure 1a. Group differences are shown in Table 12. Change from baseline in HAMD scores over time according to the LOCF analysis are shown in Table 13, group differences in Table 14, and mean scores over time in Fig 1b, Appendix 1. Treatment with citalopram gave a statistically significant higher reduction of scores at every time point, including at week 24 (p=0.03). The analysis of change in HAM-D 21 from baseline to week 24 was also performed for a number of subgroups (gender, HAM-D 21 severity at baseline, CGI severity at baseline). The subgroup analyses did not identify any statistically significant differences between the treatments.

Table 11.**Total score in HAM-D at each visit for the two treatment groups, OC analysis.**

	Visit	Treatment	n	Mean	Median	Std	Min	Max
HAM-D 21	**Baseline**	**Reboxetine**	177	27.4	27.0	3.5	22	37
		Citalopram	173	27.4	27.0	3.9	22	42
	Week 2	**Reboxetine**	154	22.1	22.0	6.0	6	36
		Citalopram	163	20.5	21.0	6.5	3	41
	Week 4	**Reboxetine**	148	17.5	18.0	6.9	3	36
		Citalopram	154	15.4	16.0	7.2	0	29
	Week 6	**Reboxetine**	139	13.8	13.0	7.4	1	35
		Citalopram	147	11.5	11.0	7.1	0	30
	Week 12	**Reboxetine**	112	9.9	9.0	7.1	0	33
		Citalopram	136	8.4	8.0	5.8	0	23
	Week 18	**Reboxetine**	105	7.7	6.0	6.4	0	32
		Citalopram	122	6.2	5.0	4.9	0	19
	Week 24	**Reboxetine**	93	6.0	4.0	5.2	0	22
		Citalopram	123	5.5	4.0	5.2	0	25
	Dropout	**Reboxetine**	67	19.1	20.0	9.4	0	36
		Citalopram	33	13.8	11.0	10.9	0	39

Table 12. **Group differences in HAM-D scores between two treatment groups at each time point, OC analysis.**

				95% Confidence Interval		90% Confidence Interval
Visit	**Estimate**	**Standard Error**	**Pr > |t|**	**Lower**	**Upper**	**Lower**
Week 2	-1.4048	0.5433	0.0102	-2.4740	-0.3356	-2.3012
Week 4	-2.0487	0.7467	0.0065	-3.5186	-0.5789	-3.2810
Week 6	-2.2097	0.8171	0.0073	-3.8185	-0.6009	-3.5584
Week 12	-1.1692	0.8466	0.1686	-2.8374	0.4990	-2.5675
Week 18	-1.4742	0.7953	0.0652	-3.0423	0.09387	-2.7884
Week 24	-0.7731	0.7711	0.3173	-2.2940	0.7478	-2.0476
Dropout	-4.0907	2.2559	0.0736	-8.5809	0.3995	-7.8453

Table 13. **Change from baseline in HAM-D scores in two treatment groups, LOCF analysis.**

Visit		Treatment	n	Mean	Median	Std	Min	Max
HAM-D 21 change from baseline	**Week 2**	**Reboxetine**	154	-5.4	-4.5	5.6	-27	7
		Citalopram	163	-6.9	-6.0	5.8	-23	3
	Week 4	**Reboxetine**	156	-9.7	-9.5	6.9	-27	6
		Citalopram	164	-11.6	-11.0	7.2	-31	5
	Week 6	**Reboxetine**	156	-13.0	-13.0	8.0	-33	9
		Citalopram	164	-15.0	-16.0	7.6	-31	0
	Week 12	**Reboxetine**	156	-15.7	-16.0	8.3	-33	9
		Citalopram	164	-17.5	-18.0	7.7	-36	0
	Week 18	**Reboxetine**	156	-17.0	-18.0	8.3	-32	9
		Citalopram	164	-19.0	-21.0	7.7	-34	0
	Week 24	**Reboxetine**	156	-17.8	-19.0	8.4	-34	9
		Citalopram	164	-19.6	-22.0	8.2	-34	0
	Dropout	**Reboxetine**	73	-8.8	-8.0	10.0	-31	10
		Citalopram	41	-12.6	-12.0	9.2	-27	6

Table 14. **Group differences in HAM-D scores between two treatment groups at each time point, LOCF analysis**

				95% Confidence Interval		90% Confidence Interval
Visit	**Estimate**	**Standard Error**	**Pr > |t|**	**Lower**	**Upper**	**Lower**
Week 2	-1.4048	0.5433	0.0102	-2.4740	-0.3356	-2.3012
Week 4	-1.9994	0.7330	0.0068	-3.4420	-0.5568	-3.2089
Week 6	-1.9418	0.8144	0.0177	-3.5446	-0.3390	-3.2856
Week 12	-1.7470	0.8516	0.0411	-3.4229	-0.07116	-3.1521
Week 18	-2.0806	0.8684	0.0172	-3.7895	-0.3716	-3.5133
Week 24	-1.8776	0.8831	0.0343	-3.6155	-0.1397	-3.3347
Dropout	-4.0446	1.9408	0.0399	-7.8987	-0.1906	-7.2691

According to the OC analysis, the mean change in MADRS from baseline to week 24 was –23.2 in both treatment groups, i.e. no difference between the treatments (p=0.881), see also Fig. 2, Appendix 1. In the LOCF analysis, the corresponding change was –18.1 for reboxetine and –20.6 for citalopram (p=0.012). For CGI, mean change from baseline was –5.0 in both groups, indicating that the treatment effect was the same (OC). The distribution of CGI-scores for severity of illness at baseline, and at week 6 and 24 is shown in Table 15. The mean total scores over time are shown in Appendix 1, Fig. 3.

Table 15. **CGI-severity of illness at baseline, week 6 and 24 for the two treatment groups (OC)**.

CGI item	Time point and treatment					
	Baseline (n)		W. 6 (n)		W. 24 (n)	
Severity of illness	RBX	CIT	RBX	CIT	RBX	CIT
Mildly ill	9	7	43	40	11	10
Moderately ill	97	84	23	31	3	4
Markedly ill	60	65	13	5	0	2
Severely ill	11	17	3	0	0	0
Total	177	173	141	151	93	124

10.1.2 The Social Adaptation Self-evaluation Scale, SASS

In the OC analysis, the mean change in SASS from baseline to week 24 was 9.1 for reboxetine and 9.2 for citalopram, see Fig. 4a, Appendix 1. Corresponding figures in the LOCF analysis were 6.4 for reboxetine and 7.9 for citalopram, see Fig. 4b, Appendix 1. No statistically significant differences were found, including a subgroup analysis of responders only. It was noticed that the scores at baseline were rather high for both treatment groups (30.2 and 30.3 respectively) compared with the scores in earlier studies of MDD. This may reflect that the current population of depressed patients was relatively well socially adapted.

An analysis of correlation between total score in HAM-D 21 and SASS showed that the scores for the two scales were highly correlated (correlation coefficient –0.53293, <0.0001).

10.1.3 Sexual function, SF

The results from the SF questionnaire, showed that men were more sexually active than women. For both gender, the sexual activity increased during the study time. In sexually active women, the prevalence of normal libido increased significantly more in the reboxetine group than in the citalopram group, Fig. 2. In the reboxetine group, the prevalence of anorgasmia decreased over the study period, while the prevalence increased in the citalopram group, the difference being statistically highly significant at week 24, Fig. 3.

Figure 2. Prevalence of normal libido among sexually active women

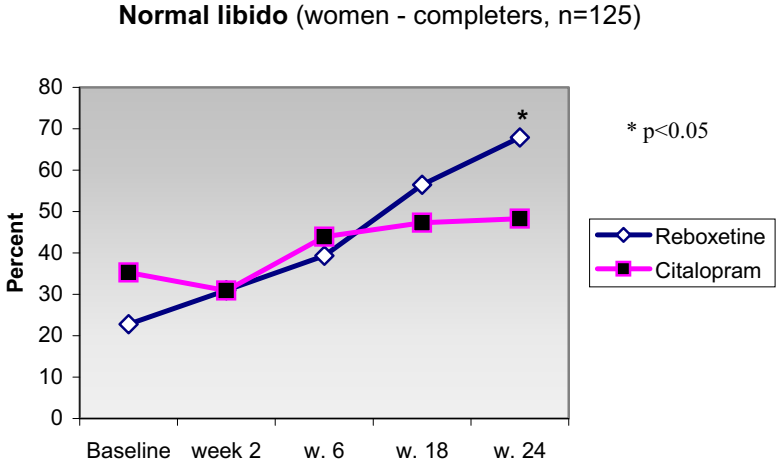
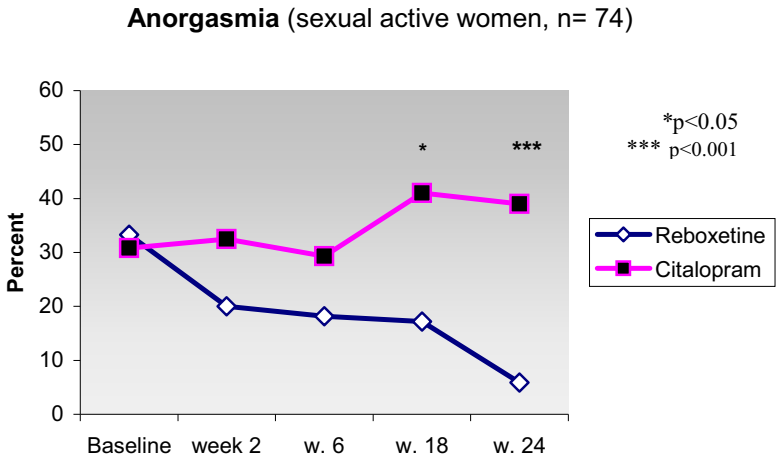


Figure 3. Prevalence of anorgasmia among sexually active women.



Among sexually active men, there was no significant difference in the prevalence of normal libido between the two treatment groups, Fig. 4. The prevalence of delayed ejaculation decreased over time in the reboxetine group, but increased in the citalopram group, Fig. 5. Rather few men reported impotence.

Figure 4. Prevalence of normal libido among sexually active men.

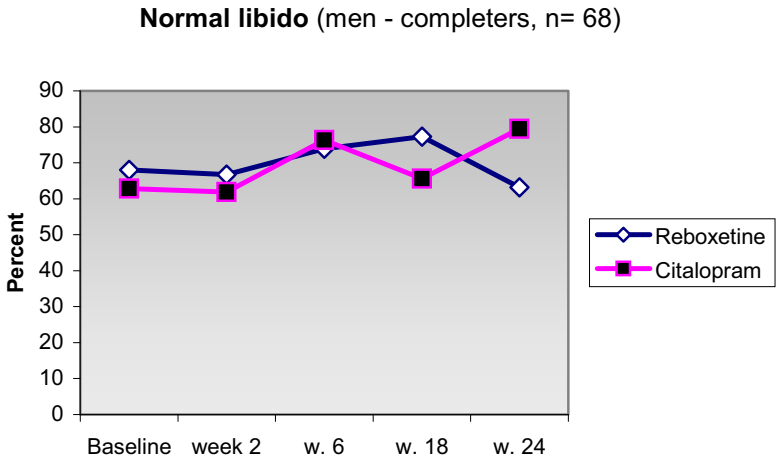
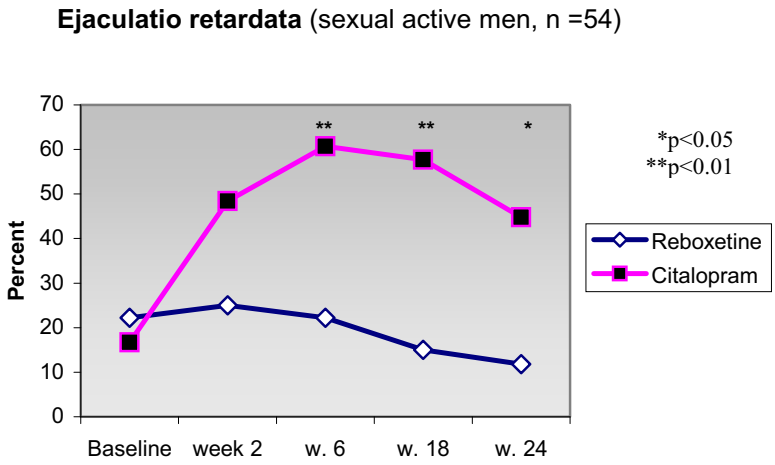


Figure 5. Prevalence of delayed ejaculation among sexually active men.



10.1.4 Response rate and remission

No statistically significant difference in response rate was detected (p=0.1215 and p=0.0577, OC and LOCF, respectively). About 90% of the patients in both groups were responding to the treatment at the week 24 visit, , see Table 16, and Appendix 1, Fig. 5. The subgroup analysis of different depression types (non-melancholic and melancholic depression; using the "melancholia index") showed similar response rates for the two treatment groups.

Table 16. **Response rates at week 24 in the two treatment groups.**

Visit		Treatment			
		Reboxetine		Citalopram	
		n	%	n	%
Week 24 (OC)	Responder	84	90.3	115	92.7
	Non-responder	9	9.7	8	6.5
	Unknown	0	0	1	0.8
	Total	93	100.0	124	100.0
Week 24 (LOCF)	Responder	115	73.2	135	82.3
	Non-responder	41	26.1	29	17.7
	Unknown	1	0.6	0	0
	Total	157	100.0	164	100.0

A statistically significant difference in remission rate was identified at the 24 weeks visit (p=0.0166 and p=0.0032, OC and LOCF, respectively) in favour of citalopram, seeTable 17, and Appendix 1, Figure 6. 79% of the reboxetine treated patients and 87% of the citalopram treated patients were in remission at the 24 weeks visit.

Table 17. **Remission rates at week 24 in the two treatment groups.**

Visit		Treatment			
		Reboxetine		Citalopram	
		n	%	n	%
Week 24 (OC)	In remission	73	78.5	108	87.1
	Not in remission	20	21.5	15	12.1
	Unknown	0	0	1	0.8
	Total	93	100.0	124	100.0
Week 24 (LOCF)	In remission	97	61.8	125	76.2
	Not in remission	59	37.6	39	23.8
	Unknown	1	0.6	0	0
	Total	157	100.0	164	100.0

The subgroup analysis of different depression types showed somewhat (non-significant) higher remission rates in the citalopram group compared with the reboxetine group (for all subgroups).

The survival analysis for days to first time in remission showed no statistically significant difference between the treatments (p=0.21).

10.1.5 Health economics

This section contains a preliminary analysis of the health economic data collected in the trial. The analyses in this section focus on differences in health care resource utilization between the two groups. The aim of the health economics component of this study was to make a cost-effectiveness (CE) evaluation of reboxetine vs citalopram. However, before doing a comprehensive CE analysis it is appropriate to first conclude whether there is a difference in resource utilization, and hence costs.

At this stage the results are primarily presented in terms of descriptive statistics in order to conclude whether any differences was evident between the two groups. The results are divided into three parts: outpatient resource utilization (visits to physician or nurse), inpatient resource utilization (number of days in hospital) and days off work (number of sick leave

days). As a first step the analyzes are based on observed data (i.e. no adjustment is made for differences in time in study or equivalently, time before withdrawal due to adverse events or lack of efficacy).

Table 18 presents the results for outpatient health care utilization using a pooled analysis of the data (ie. all data from Denmark, Finland and Sweden). Based on the simple arithmetic means, the results do not show any differences between the groups. There is a tendency for lower values for the citalopram group for all categories of outpatient visits, although the absolute levels are low in both groups. In an analysis by country (results not shown), the pattern is similar with small differences in all cases. It should be noted that since the time in study was shorter in the reboxetine group, the results in the table underestimates the level of outpatient health care use in the reboxetine group.

Table 18. **Outpatient visits. All patients**

Group		GP	Other specialist	Nurse	Other
Reboxetine	N	177	177	177	177
	Mean	0.53	0.30	0.16	0.34
	Sum	93	53	29	60
Citalopram	N	173	173	173	173
	Mean	0.33	0.26	0.08	0.20
	Sum	57	45	13	34

As a measure of inpatient health care utilization we collected data on the number of days in hospital in the CRFs. As could be expected, the mean number of days in hospital was low and similar in both groups. The number of patients that were hospitalized during the study was also low (reboxetine 4 cases, citalopram 6 cases). Hence, no differences in hospitalization costs can be infered from the data, see Table 19.

Table 19. **Days in hospital.**

	Reboxetine	Citalopram	Both groups
N	177	173	350
Mean	0.13	0.13	0.13
Sum	23	23	46

As a measure of indirect costs we collected data on the number of days patients were not able to work. The results are shown in Table 20 using data from patients categorized as employed (or on sickleave) at baseline.

Table 20. **Days off work. Pooled analysis of Swedish, Danish and Finnish data**

	Reboxetine	Citalopram	Both groups
N	105	114	219
Sum	761	1 172	1 933
Mean	7.24	10.28	8.82
Std. Deviation	13.90	24.17	19.93

The point estimates show that the reboxetine group had fewer days off work than the citalopram group. This difference was however not statistically significant based on a t-test analysis (p = 0.53). Since the time in study was lower for the reboxetine group we also made an additional analysis adjusting for time in study, Table 21

Table 21. **Days off work. Data adjusted for time in study**

	Reboxetine	Citalopram	Both groups
N	105	114	219
Sum	1 875	1 760	3 635
Mean	17.86	15.44	16.60
Std. Deviation	33.80	34.27	33.99

Using a measure adjusted for time in study, the results are different compared to the analysis based on observed data. In Table 21, it is clearly seen that the mean number of days off work are now higher in the reboxetine group, indicating a higher cost due to sick-leave. However, based on a t-test this difference is not statistically significant (p = 0.6) and we thus conclude that the two groups are equal with respect to impact on sick-leave due to illness.

10.1.6 Efficacy Conclusions

In the LOCF analysis of the primary endpoint at week 24, citalopram displayed statistically significantly better efficacy than reboxetine. When data was analysed it was, however, concluded that the LOCF analysis was not valid since there was a huge amount of missing data. Most of the missing data were due to early drop-outs. Another reason for not using the LOCF was that the treatment effect was increasing over time, which would have been

ignored in an LOCF analysis. The OC was therefore considered to be the most valid analysis for the primary efficacy variable.

The results seen in the OC analysis did not display any statistically significant differences in efficacy between the two treatment groups. In the OC analysis of the primary endpoint at week 8, the mean change from baseline in the 17-Item HAM-D total score was –15.2 in both treatment groups. None of the secondary endpoints, except HAMD remission rate, showed a statistical significant difference between the two different groups.

10.2 Safety Results

10.2.1 Adverse Events

The number of TES was 185 in the reboxetine group compared to 155 in the citalopram group. These TES occurred in 51% of the reboxetine patients and 40% of the citalopram patients. The most frequently reported adverse event (spontaneous and according to the UKU scale) among the reboxetine-treated patients were: dry mouth (15.7%), constipation (12.2%), tendency of sweating (11%), insomnia (7.1%), nausea (5.8%), increased dream activity (5,7%), headache (5.7%), orthostatic dizziness (5.2%), and micturation disturbances (5.2%). In the citalopram group, the most frequently reported adverse events were: orgastic dysfunction (13.2%), nausea (7.1%), dizziness (5.6%), and influenza like symptoms (5.1%), see Appendix 2, Fig. 1 and Tab. 1. The majority of adverse events reported by patients in both treatment groups were mild to moderate in intensity.

Serious adverse events were reported in 4 reboxetine-treated patients and 4 citalopram-treated patients. In the reboxetine group, the following serious adverse events were reported: 2 suicidal attempts, 1 abdominal pain, and 1 hypertension. In the citalopram group, the following serious adverse events were reported: 2 suicidal attempts, 1 pregnancy unintended and 1 alcohol problems. None of these SAE's were judged as drug related. No deaths were reported during this study.

10.2.2 Clinical Laboratory Evaluation and Vital Signs

A review of the descriptive statistics of the laboratory analyses revealed that there was no clinically significant difference between the treatment groups in any of the laboratory parameters.

No statistically significant differences were observed between the two treatment groups in the physical examinations including change in systolic or diastolic blood pressure. A statistically significant increase in pulse rate was noted in the reboxetine group. At week 24, the mean change from baseline pulse rate was +6 beats per minute in the reboxetine group (average pulse range at w. 24: 50-112 per min.), and -2 beats per minute in the citalopram group (average pulse range at w. 24: 46-97 per min.). No statistically significant differences

were observed between treatment groups in the mean change from baseline body weight at all visits.

10.2.3 Exposure in Utero

There were no known pregnancies during this study (one pre-study pregnancy was revealed at screening) .

10.2.4 Safety Conclusions

No statistically significant differences were observed between treatment groups in the physical examinations, including change in systolic or diastolic blood pressure. A small increase in pulse rate was noted in the reboxetine group. This may possibly be due to a weak sympathomimetic effect, or a weak, secondary anticholinergic effect (vagolytical).
The adverse-event profiles that were observed for reboxetine and citalopram in this study are consistent with the profile established in previous studies. The majority of adverse events that were reported by patients in each treatment group were mild to moderate in intensity. Only four SAEs were reported in each treatment group. The percentage of patients who discontinued treatment due to adverse events was higher in the of the reboxetine group than in the citalopram group. As relatively many of the withdrawals were noted in the first weeks of treatment they may have been a consequence of the high (full dose, 8 mg/day) starting dose. Results from a recent study [29] indicate that lower starting dose (i.e. 4 mg reboxetine per day) leads to fewer side-effects and fewer drop-outs.

10.2.5 Treatment Compliance

Due to misunderstanding of the correct way to fill in the Drug dispensation data in the CRF:s at some of the centers, an exact level of compliance cannot be calculated. According to the monitors and the investigators, the compliance was acceptable.

11 DISCUSSION AND OVERALL CONCLUSIONS

Baseline data and demographics were well balanced between the treatment groups, meaning that the descriptive statistics indicated equivalent groups regarding prognostic factors such as age, gender and HAM-D 21 total score. According to the sample size calculations, 150 patients were needed in each treatment group. However, only 93 reboxetine patients and 123 Citalopram patients completed the 24 weeks study. This fairly large drop-out rate gave a loss of statistical power which may jeopardize the validity of the study.

When data was analysed it was concluded that the LOCF analysis was less valid since there was a huge amount of missing data, mostly due to a relatively high number of early drop-outs. Another reason for not using the LOCF was that the treatment effect was increasing over time, which would have been ignored in an LOCF analysis. The OC was therefore the only analysis considered valid for the primary efficacy variable.

The number of Treatment Emergent Symptoms (TES) was 185 in the reboxetine group compared to 155 in the citalopram group. There were 4 serious AES in each treatment group. The adverse event profile that was observed for reboxetine in this study is consistent with the profile that was established in previous studies. There was a significantly higher prevalence of sexual side-effects in the citalopram group, both among women and men. No new safety concerns associated with the use of reboxetine were identified.
Overall, the patient population in this study was reflective of the general population of patients with depression. In the CGI registration at baseline, it was evident that rather few patients were classified as having “severe illness”. This may have influenced on the results, as reboxetine earlier was reported to have superior efficacy compared with fluoxetin efficacy in patients with severe MDD.

The relatively high rate of reboxetine discontinuations during the first weeks of treatment was mainly due to drug-related side effects. This is judged to be the result of a non-titration starting dose of 8 mg per day. In a recent clinical trial, reboxetine was administered at 4mg during the first week of treatment, and the number of discontinuations due to adverse events was much lower than in CT’s using 8 mg as starting dose. Thus, the lack of reboxetine dose escalation may have contributed to the high number of discontinuations due to adverse events in the current study. The OC statistical analysis of the primary efficacy variable concludes that reboxetine is non-inferior to citalopram regarding the efficacy.

12 ACKNOWLEDGEMENTS

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APPENDICES

APPENDIX 1. Efficacy Results

APPENDIX 2. Adverse Events

APPENDIX 1. EFFICACY RESULTS

Fig. 1 a. HAM-D 21, total scores over time in the two treatment groups (OC).

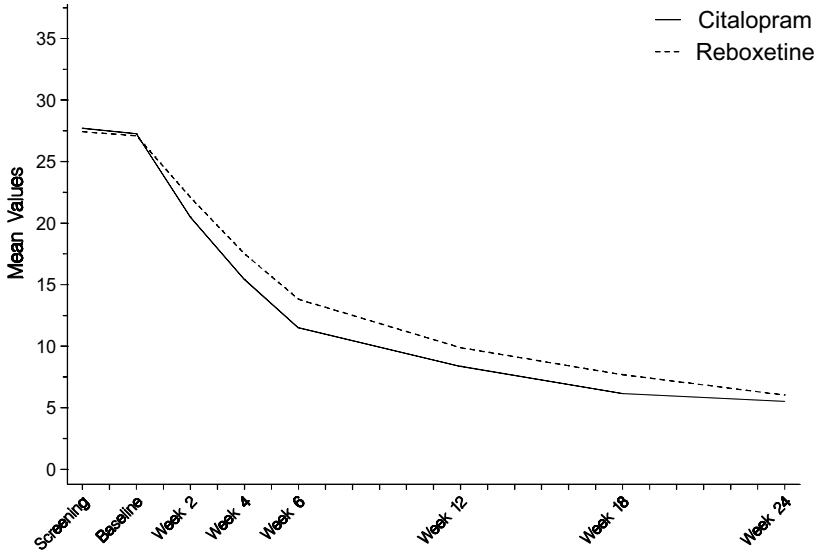


Fig. 1 b. HAM-D 21, total scores over time in the two treatment groups (LOCF).

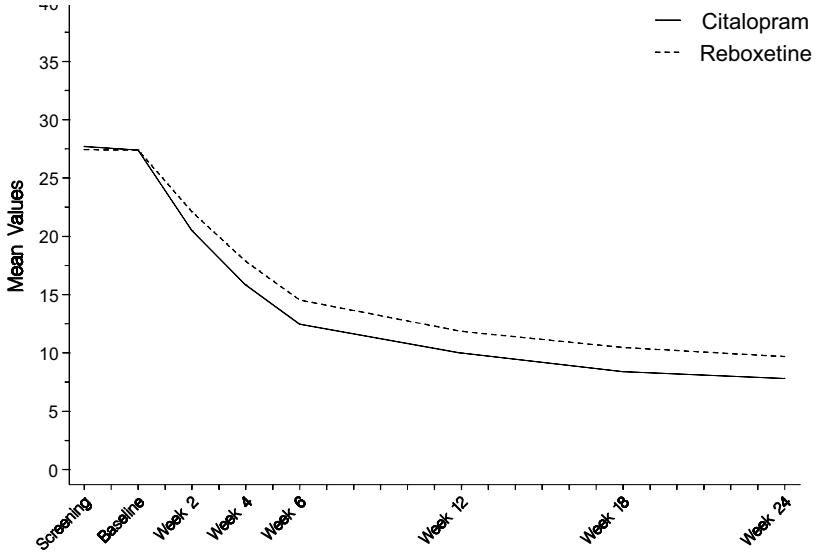


Fig. 2a. MADRS, total scores over time in the two treatment groups (OC).

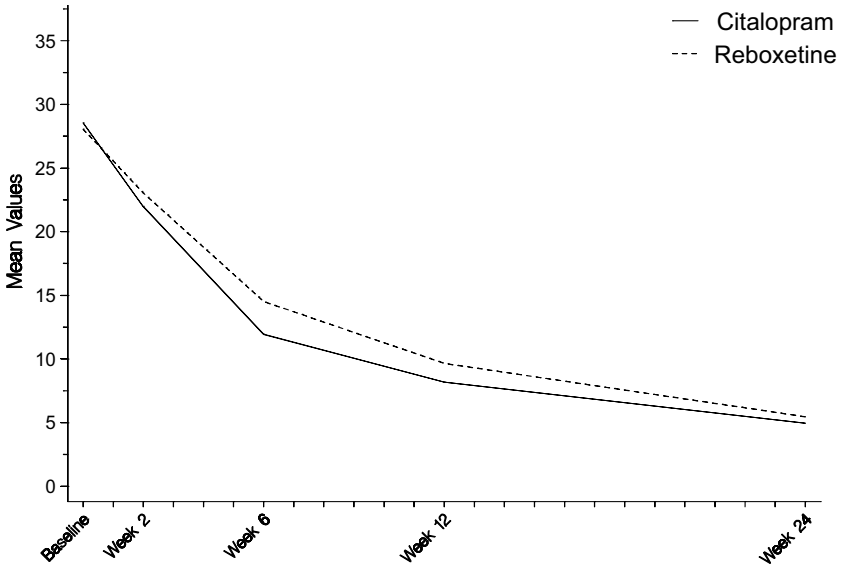


Fig. 2b. MADRS, total scores over time in the two treatment groups (LOCF).

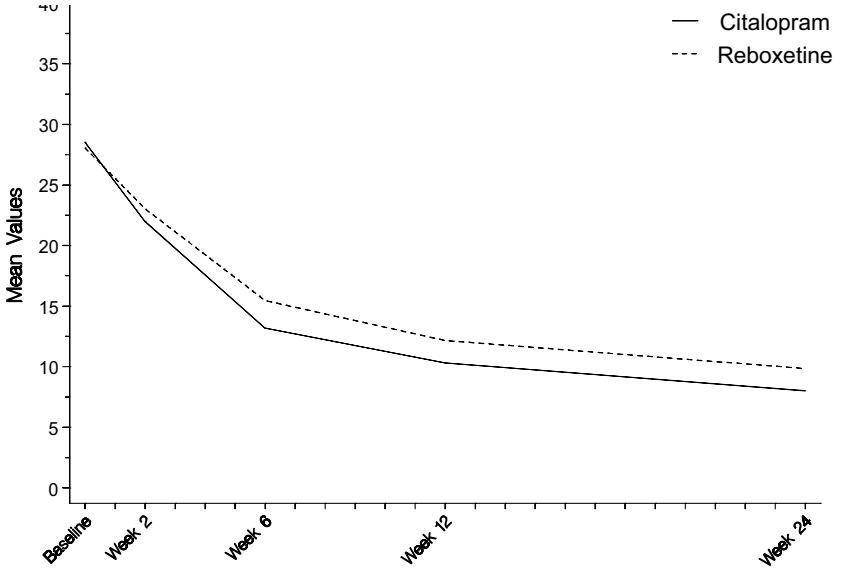


Fig. 3. CGI (severity of illness) total scores over time in the two treatment groups (OC).

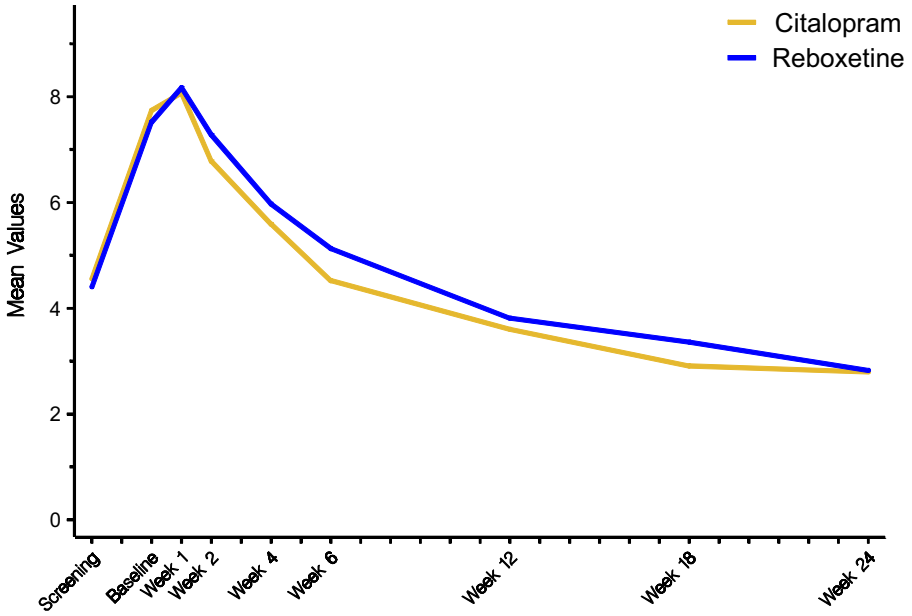


Fig. 4a. SASS, total scores over time in the two treatment groups (OC).

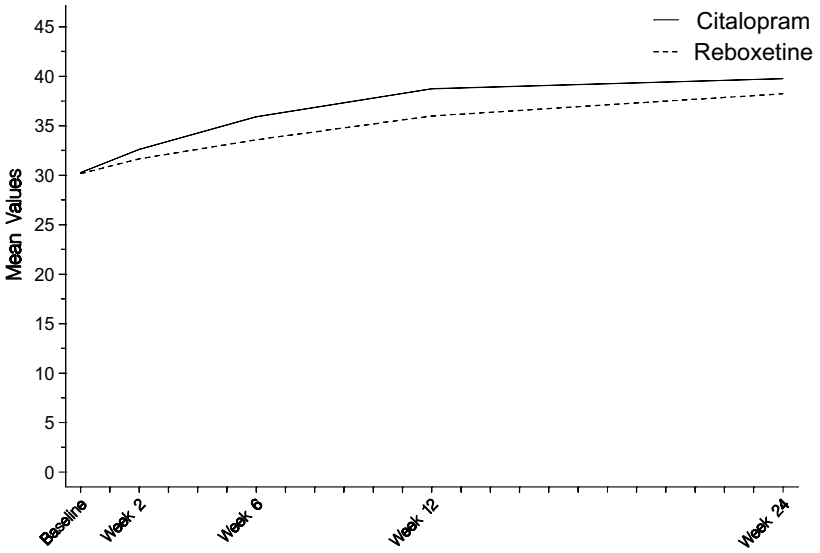


Fig. 4b. SASS, total scores over time in the two treatment groups (LOCF).

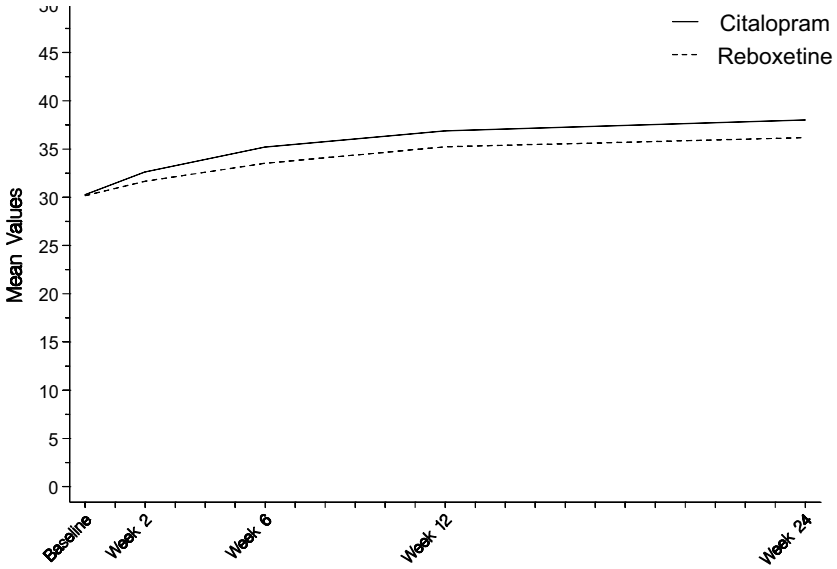


Fig. 5a. Response rates over time in the two treatment groups (OC)

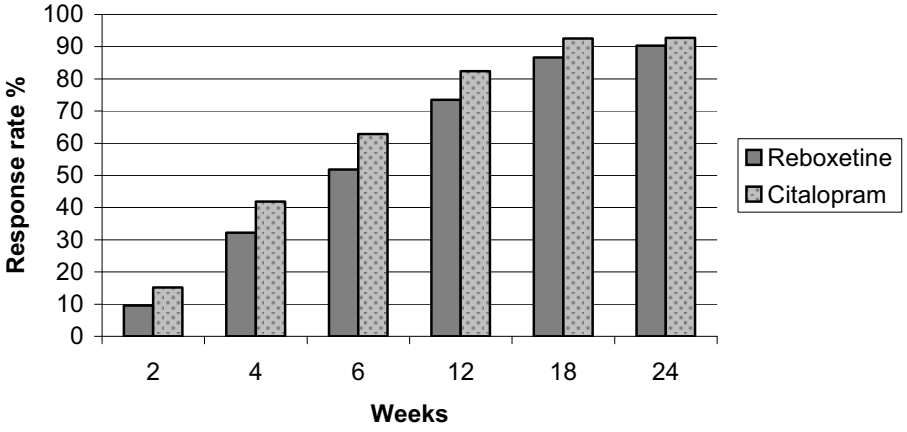


Fig. 5a. Response rates over time in the two treatment groups (LOCF)

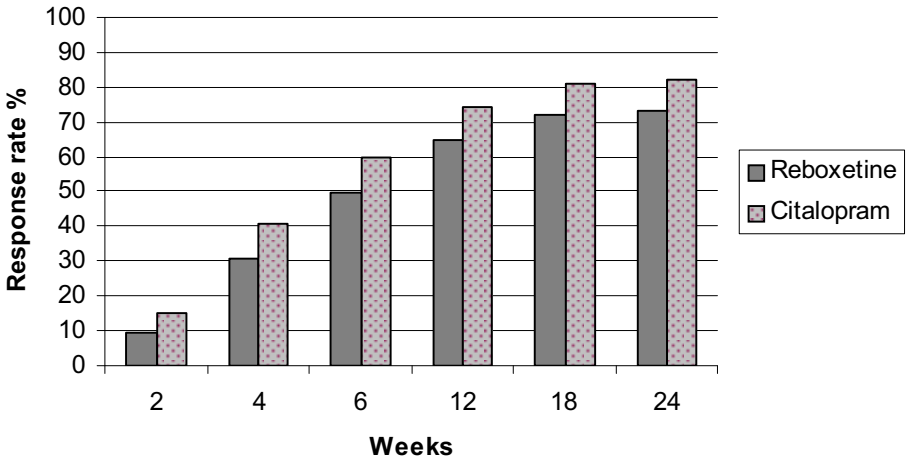


Fig. 6a. Remission rates over time in the two treatment groups (OC)

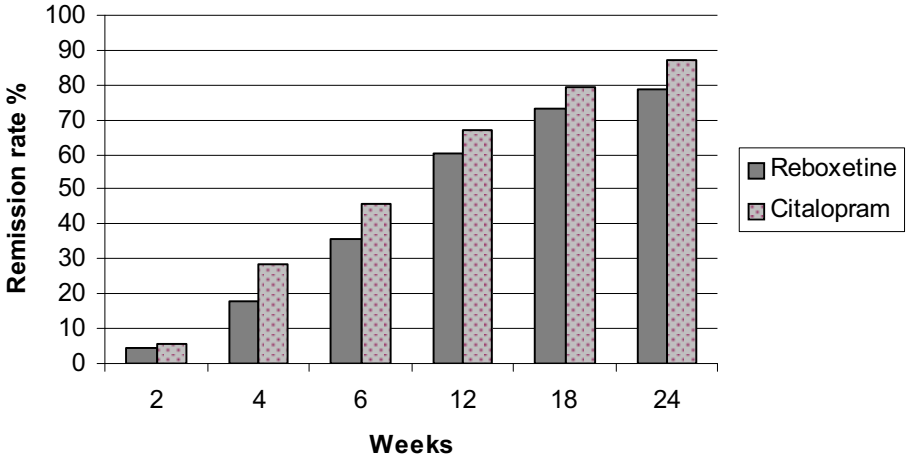
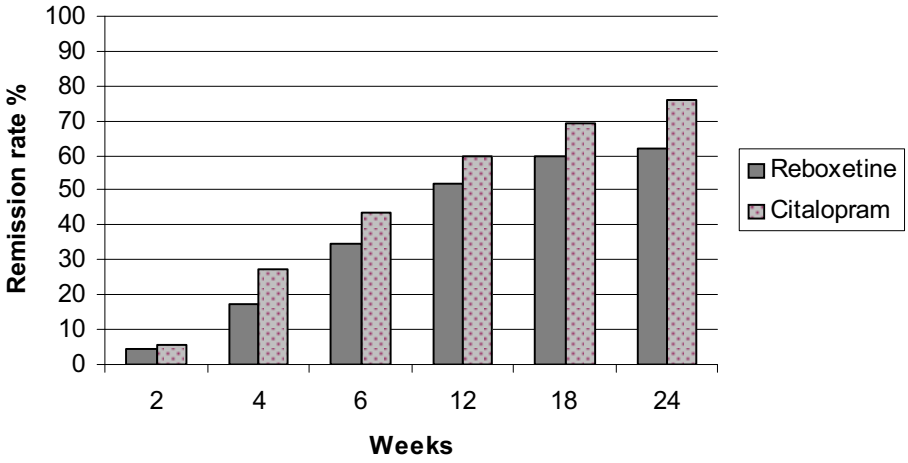


Fig. 6a. Remission rates over time in the two treatment groups (LOCF)

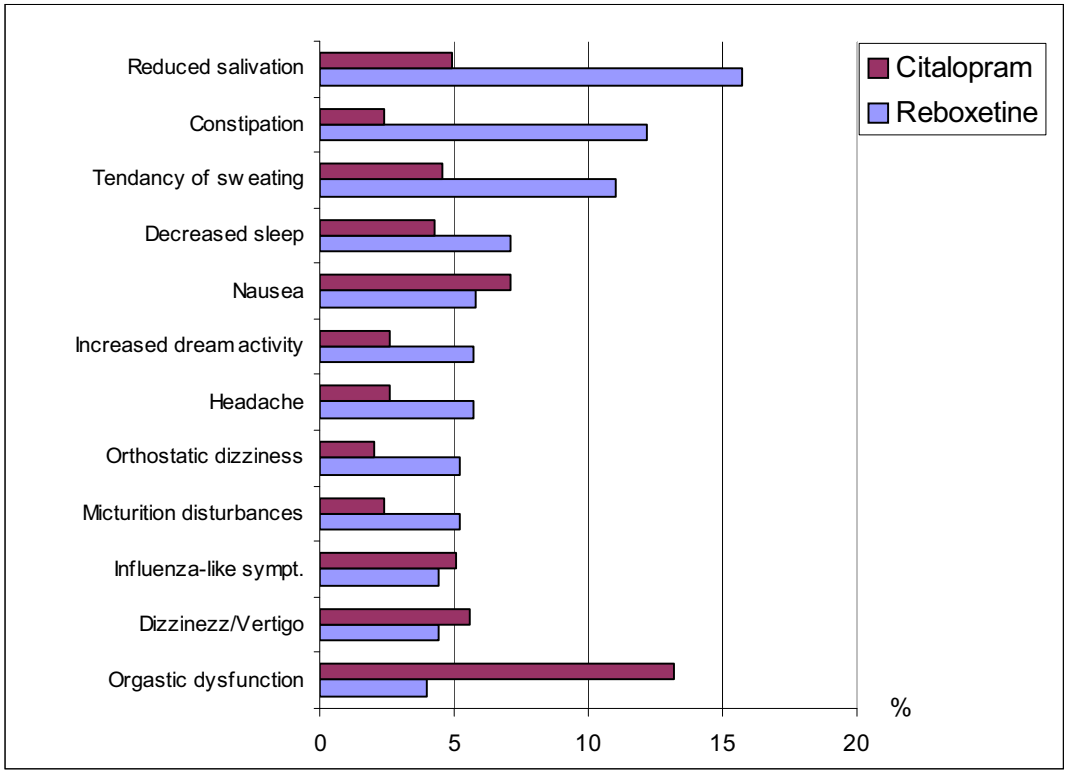


APPENDIX 2. ADVERSE EVENTS

Table 1. Frequency (%) of adverse events in the two treatment groups

	Reboxetine	Citalopram
Confusion	1,2	0,7
Increased salivation	1,2	0
Weight gain	1,4	1,5
Concentration difficulties	1,7	1,2
Palpitations/tachycardia	1,7	1,8
Tension/inner unrest	1,7	2,2
Diarrhoea	1,9	1,8
Diminished sexual desire	1,9	3
Failing memory	1,9	1,2
Increased sleep	1,9	3,7
Accomodation disturbance.	2,1	0,7
Emotional indifference	2,3	0,6
Rash	2,3	1,3
Paraesthesia	2,8	2,8
Upper resp. tract infect.	2,8	4,5
Tremor	2,9	1,3
Orgastic dysfunction	4	13,2
Polyuria/polydipsia	4,1	2,6
Weight loss	4,4	0,7
Dizzinezz/Vertigo	4,4	5,6
Insomnia	4,4	3,4
Influenza-like symptoms	4,4	5,1
Sedation	4,7	4,7
Micturation disturbances	5,2	2,4
Orthostatic dizziness	5,2	2
Headache	5,7	2,6
Increased dream activity	5,7	2,6
Nausea	5,8	7,1
Decreased sleep	7,1	4,3
Tendency of sweating	11	4,6
Constipation	12,2	2,4
Reduced salivation	15,7	4,9

Figure 1. Frequency (%) of the most common adverse events in the two treatment groups.


Reduced salivation
Constipation
Tendancy of sw eating
Decreased sleep
Nausea
Increased dream activity
Headache
Orthostatic dizziness
Micturition disturbances
Influenza-like sympt.
Dizzinezz/Vertigo
Orgastic dysfunction
Citalopram
Reboxetine
%
0
5
10
15
20