Integrated Clinical Study Report

A double-blind study comparing citalopram tablets (Lu 10-171, 10-40 mg per day) and placebo in the treatment of major depression in adolescents

Investigational Product: Citalopram

Clinical study ID:	94404
Phase of development:	Phase III
Indication:	Major depression
First patient first visit:	19 November 1996
Last patient last visit:	23 April 2001
Investigators:	31 recruiting investigators in 7 countries *Signatory Investigator*: Professor Anne-Liis von Knorring, M.D., Uppsala, Sweden
Study centres:	31 recruiting centres in 7 countries: 3 in Denmark, 2 in Estonia, 12 in Finland, 2 in Germany, 3 in Norway, 7 in Sweden, and 2 in Switzerland
Sponsor:	International Clinical Research H. Lundbeck A/S DK-2500 Copenhagen-Valby, Denmark
Study director:	Karoline Als, M.Sc. Pharm., H. Lundbeck A/S
Report No. and date:	236/311, 2001, 21 March 2002

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

4 Study Objectives

As stated in the protocol (Appendix I.1), the objectives of the study were as follows:

Primary Objective

- to study the efficacy and tolerability of citalopram compared to placebo in adolescent patients suffering from major depression

Secondary Objective

- to investigate the Expressed Emotions (EE)

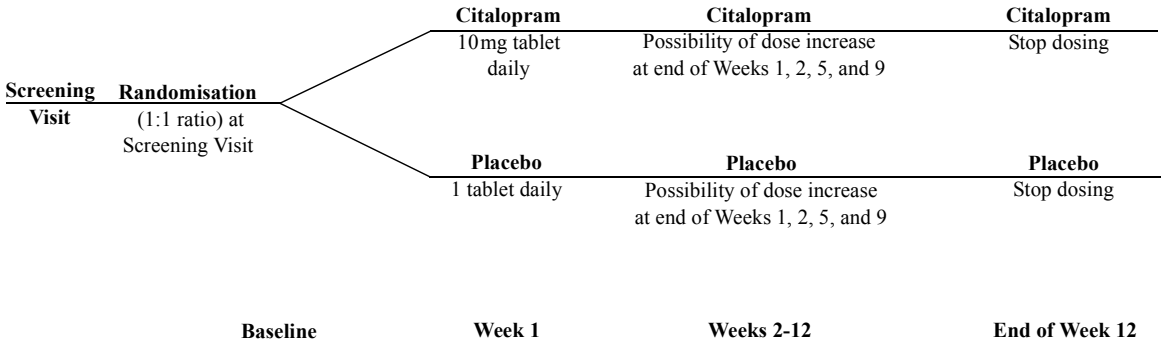
5 Investigational Plan

5.1 Overall Study Design and Rationale

Study Design

This was a multinational, multicentre, randomised, double-blind, parallel-group, placebo-controlled, flexible-dose study.

The overall study design is seen in Panel 1.



Panel 1 Overall Study Design

Rationale for Study Design

The parallel-group, placebo-controlled design with a 12-week duration was a standard design for studies on depression at the time the study protocol was approved.

The study was designed to comply with the CPMP Note for Guidance on Good Clinical Practice[2] and Directive 91/507/EEC. During the study, the ICH guideline for Good Clinical Practice was issued and therefore implemented in the conduct of the study.[3]

Variables for Evaluation

- *Efficacy* – Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present Episode Version, depression module (Kiddie-SADS-P) total score; Montgomery and Åsberg Depression Rating Scale (MADRS) total score (implemented 9 months after study start); Becks Depression Inventory (BDI); Global Assessment of Functioning (GAF); Life Event Scale (LES)

- *Expressed emotions* – Five Minute Speech Samples
- *Serum concentrations* – serum concentrations of citalopram and its metabolites, DCT and DDCT
- *Pharmacodynamics* – correlation between serum concentrations and response on primary efficacy variable
- *Safety* – adverse events (AEs), Utvalg for Kliniske Undersøgelser (UKU) symptom checklist, clinical laboratory tests, ECGs, weight, vital signs, and physical examinations

Study Population

A minimum of 220 patients evaluable for the efficacy analyses were planned for enrolment into two parallel arms, with 110 patients per arm.

The inclusion and exclusion criteria were chosen to select adolescent outpatients with major depression according to the DSM-IV criteria,[15] with a duration of the present episode of at least 4 weeks and up to one year, and who had a BDI score ≥21 and a GAF score ≤60 at the screening visit. The entry criteria were changed during the study (as described in protocol amendment No. A3 and in Panel 6) to in- or outpatients, and to BDI score ≥21 for girls and ≥16 for boys, and to GAF score ≤60 for any of the four items assessed. The rationale behind these criteria was to ensure that patients had a clinically relevant severity of depressive symptoms at inclusion.

Treatments

The dose range of citalopram (10 to 40 mg) was chosen because citalopram is safe and well tolerated in this dose range in adults. Daily dosing was justified as the terminal half-life of citalopram in humans is about 1.5 days.[16] Placebo treatment was considered necessary for demonstrating short-term efficacy.

5.2 Study Population

5.2.1 Selection Criteria

Patient selection was based on the inclusion and exclusion criteria listed below.

Inclusion Criteria

Patients who met each of the following criteria were eligible for the study:

1. Both patient and guardian(s) had given written informed consent.

Screening Visit

At the Screening Visit, written informed consent was obtained and the patient's demographic data and the essential features of major depression according to the DSM-IV criteria were reviewed. The patient completed the BDI self-rating questionnaire, and assessment of the GAF score was done. In addition, a 5 minute interview (Five Minute Speech Sample, FMSS) with each parent was recorded on tape for subsequent analysis of Expressed Emotions (EE). Concomitant medication was reviewed. A blood sample was obtained for clinical laboratory tests and an ECG was recorded. The patient was reviewed against the entry criteria.

Baseline Visit

The results of the screening ECG and clinical laboratory tests were reviewed. A physical examination including vital signs, height, and weight was performed, and adverse events/UKU symptom checklist and concomitant medication were recorded. The patient's medical, psychiatric, and social history were obtained. The family background was penetrated. The Life Event Scale (Severity of Psychosocial Stressors Scale (adolescents)) was completed. The Kiddie-SADS-P interview was performed and the MADRS was assessed. The trial medication was dispensed.

Other Visits

At all visits, a physical examination, including vital signs, was performed. In addition, adverse events/UKU symptom checklist, concomitant medication, and other treatment (psychotherapy) were recorded. The patient completed the BDI self-rating questionnaire, and assessment of the GAF score was done. From Week 1 and onwards, returned study product was collected and dose increase criteria were reviewed. Study product was dispensed at each visit. With respect to the scheduling of Kiddie-SADS-P scoring, Life Event Scale completion, laboratory tests, serum concentration samples, and ECG recording, please refer to the flow chart in Panel 4.

5.6 Efficacy Assessments

The primary measure of efficacy was based on the Kiddie-SADS-P total score. The secondary measures of efficacy were the BDI, MADRS, GAF, and LES scores. EE was analysed for possible influence on the Kiddie-SADS-P total score. The BDI and GAF scores were used as entry criteria (see section 5.2.1). The GAF score was also used to justify dose adjustments (see section 5.3.1).

Schedule for Affective Disorders and Schizophrenia for School Aged Children (Kiddie-SADS-P)

The depression module of the Kiddie-SADS-P rating scale is a used and validated schedule in assessing depression in children and adolescent patients.[17] The Kiddie-SADS-P is a semi-structured diagnostic interview, designed to record information regarding a child's or an adolescent's functioning and symptoms for the current episode of a psychiatric disorder. In this study, the 9-item scale was used and the depression items were used for the assessment of efficacy. Patients with a score ≤2 on the depression and anhedonia items (items IA and III, respectively) were defined as responders. Patients with a score ≥3 on either the depression or the anhedonia items were defined as non-responders.

The raters were trained in the use of the Kiddie-SADS-P scale in co-rating sessions (see Appendix I.4 for a list of persons trained at the rater sessions).

Montgomery and Åsberg Depression Rating Scale (MADRS)

The MADRS[18] consists of 10 items, each with ratings on a scale from 0 (no symptoms) to 6 (severe symptoms). All items are core symptoms of the depressive episode and thus measure the severity of the depressive episode since the previous visit.

Beck's Depression Inventory (BDI)

The BDI[19] was originally made for measuring changes in depressive symptoms but has also been validated for depression screening. The BDI consists of self-evaluative statements in 21 categories.

Five Minutes Speech Sample (FMSS)

The FMSS is a method for assessing the attitudes and feelings that a relative expresses about a mentally ill family member (Expressed Emotions (EE)).[20] The examiner that administers the task does not require training in the coding system while the rater that analyses the speech needs to be trained.

5.7 Serum Concentrations of Citalopram and Its Metabolites

To obtain information about the actual concentrations of citalopram and its metabolites, blood samples (2 × 7 ml venous blood) were taken at the Week 1 and 12 visits. Blood samples could also be taken in the case of serious adverse events, withdrawals, or if the dose was reduced. The samples were to be taken in the morning before dosing and the date and time was to be recorded in the CRF.

from Day 5-14 were treated as Week 1 samples. Likewise, samples drawn at Days 74-105 were treated as Week 12 samples.

After dose increase, a titration period of 4 days, that is, 3 doses, of the increased dose was required before the new dose was recorded as the current dose. If the titration period was less than 4 days, the previous dose was used in the analysis. The serum concentrations obtained after dose discontinuation were considered in the pharmacokinetic evaluation, if only one dose was omitted, for example, no dose had been taken the evening before the blood sampling. If the discontinuation period was more than 2 days, that is, more than one dose was omitted, the serum concentration was excluded from the pharmacokinetic evaluation. The samples from patients who were treated with placebo were ignored in the pharmacokinetic evaluation.

Serum concentrations below the lower limit of quantification (LOQ) were not plotted. In the calculation of descriptive statistics, the concentrations below the LOQ contributed with a value of ½ LOQ.

6.7 Efficacy Analysis

6.7.1 Efficacy Parameters

Primary Efficacy Endpoint

The primary efficacy parameter was:

- change from baseline in the Kiddie-SADS-P total score over time

Secondary Efficacy Endpoints

The secondary efficacy endpoints were:

- change from baseline to each visit and to final assessment in the Kiddie-SADS-P total score
- Kiddie-SADS-P response at each visit and at final assessment. Kiddie-SADS-P response/non-response was defined as:
  - response when items "depression" and "anhedonia" were ≤2
  - non-response when either "depression" or "anhedonia" were ≥3
- change from baseline in the MADRS total score over time
- change from baseline to each visit and to final assessment in the MADRS total score
- MADRS response at each visit and at final assessment. MADRS response was defined as at least a 50% reduction from baseline in the MADRS total score.
- MADRS remission at each visit and at final assessment. MADRS remission was defined as MADRS total score ≤12.
- changes from baseline in the BDI, GAF and LES scores

6.7.2 Analysis of Efficacy Parameters

Primary Efficacy Analysis

The primary efficacy analysis was a repeated measures analysis of change from baseline in the Kiddie-SADS-P total score. The analysis was performed on the FAS on observed cases (OC).

Initially, the model included the following factors: baseline score, treatment, time, time squared, and treatment by time. All factors were treated as fixed effects. The time squared factor was omitted from the model if not statistically significant at the 5% level. Treatment comparisons were then made using the reduced model.

The treatment by time factor was tested first to compare the treatment effect over time. Statistical significance at the 5% level would establish whether the response profile over time for citalopram was different from that of placebo. Failure to detect statistical significance would imply that the change over time for the two groups was parallel after Week 2. The test for treatment effect was then based on the main treatment variable at the 5% level.

The above model was used first with an unstructured variance covariance matrix since it was expected to provide the best fit of the data (due to the relatively low number of repeated measurements within patients). Other covariance structures like compound symmetry and random effects were studied. The different covariance structures were compared using likelihood ratio tests and Akaike's information criterion.

If the treatment by time interaction was significant at the 5% level, the treatment effect along with the 95% confidence interval at Week 12 was estimated.

As a next step, centre was included in the model to test for centre effect. If significance was found at the 10% level for either centre or one of the factors with centre, this finding was described, but the analysis result based on the model without centre was regarded as the main result.

Secondary Efficacy Analyses

The changes from baseline to:

- final assessment in the Kiddie-SADS-P total score using last observation carried forward (LOCF)
- each visit in the Kiddie-SADS-P total score using OC
- final assessment in the MADRS total score using LOCF
- each visit in the MADRS total score using OC

were analysed for the FAS. The analyses were based on a general linear model for analysis of covariance (ANCOVA) with factor treatment and baseline scores as covariates. The

differences between treatments were estimated with a 95% confidence interval. In addition, the change from baseline to final assessment in the MADRS total score was analysed (ANCOVA), including the explanatory variables age, sex, BMI, weight, and centre.

The change from baseline in the MADRS total score was analysed by repeated measures using the same method as in the primary analysis of efficacy.

Using Fisher's exact test, treatment groups were compared for the proportion of patients that:

- at each visit and at final assessment had Kiddie-SADS-P response
- at each visit and at last assessment had MADRS response
- at each visit and at final assessment had MADRS remission

For definitions of response and remission, see section 6.7.1.

Descriptive statistics were presented for the BDI total scores, GAF mean scores, and Life Event Scale scores and treatment differences in adjusted mean changes for BDI total scores, GAF mean scores, and Kiddie-SADS-P single item scores were analysed (ANCOVA).

Pharmacodynamic Analysis

An explanatory analysis was performed in order to examine any correlation between serum drug concentrations and response on the primary efficacy variable.

Expressed Emotions Analysis

The distribution of the FMSS scores (high or low) were tabulated. To explore whether expressed emotions had an influence on efficacy, the FMSS score was added as an explanatory variable to the primary efficacy analysis.

6.7.3 Handling of Missing Data and Withdrawals

For analyses using LOCF, missing values for post-baseline Kiddie-SADS-P and MADRS assessments were imputed by the last observed value immediately prior to the missing value. If the number of missing items was less than two, the total score was calculated as: the sum of non-missing items times the total number of items divided by the number of non-missing items. If more than three items were missing, the total score was regarded as missing.

6.7.4 Adjustments for Multiple Comparisons

Since the primary efficacy analysis was only between citalopram and placebo, no attempt was made to adjust for multiple comparisons. Only the p-value from the primary analysis was

7 Patients

7.1 Patient Disposition

Patient disposition and the data sets used for the analyses are summarised in Panel 7. A total of 244 patients were randomised into the study (APRS), 233 patients took at least one dose of double-blind treatment (APTS) and approximately two-thirds completed the study. Four patients in the placebo group and 6 patients in the citalopram group were withdrawn after the first dose but prior to the first post-baseline Kiddie-SADS-P assessment. Thus, a total of 223 patients comprised the FAS. A summary of patient disposition by centre is shown in Table 2 and patient disposition by treatment group and visit is tabulated in Table 3. At a classification meeting held prior to unblinding of the study, the patients were classified into the various data analysis sets. Listing A.2 identifies the patients that were excluded from the various datasets.

Panel 7 Summary of Patient Disposition (APRS)

	PBO		CIT		All	
	n	%	n	%	n	%
Patients Randomised (APRS)	120		124		244	
Patients Treated (APTS)	112		121		233	
Patients Completed	74	66.1%	79	65.3%	153	65.7%
Patients Withdrawn from APTS	38	33.9%	42	34.7%	80	34.3%
Efficacy Data Sets:						
Full Analysis Set (FAS)	108		115		223	
Per Protocol Set (PPS)	91		104		195	

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The frequencies of patients withdrawn from the study are tabulated by primary reason in Panel 8. Withdrawal for any reason was similar in the two treatment groups; approximately one-third of the patients withdrew. Adverse events contributing to withdrawal were always regarded as the primary reason for withdrawal; see section 6.4. Overall, the most common primary reasons for withdrawal were lack of efficacy and adverse events. Withdrawal due to lack of efficacy was more common in the placebo group (16%) than in the citalopram group (9%), whereas adverse events were a slightly more common reason for withdrawal in the citalopram group (13 patients, 11%) than in the placebo group (9 patients, 8%). None of these differences were of statistical significance (see Appendix I.9). Some patients had more than one reason for withdrawing from the study and all contributory reasons are summarised by treatment group in Table 5. A listing of all patients who withdrew from the study is in Listing A.1. It should be noted that the primary reasons for withdrawal in Listing A.1, are the reasons indicated by the investigators.

9 Efficacy Evaluation

9.1 Data Sets Analysed

All efficacy analyses were conducted on the FAS. No efficacy analyses were conducted for the PPS since the number of patients in this set did not differ from that in the FAS by more than 20% (see section 11.1 of the Statistical Analysis Plan, Appendix I.9).

Individual patient scores on the Kiddie-SADS-P, MADRS, BDI, GAF, and LES are given by centre, treatment group, and patient number in Listing A.11 to Listing A.15.

9.2 Drug Concentration and Relationship to Response

The tabulated serum levels and the corresponding plots are in Table 20 (citalopram), Table 21 (DCT), and Table 22 (DDCT) and Figure 4 (citalopram), Figure 5 (DCT), and Figure 6 (DDCT).

Figure 7 is a plot of the relationship between the citalopram serum concentrations obtained at Week 12 and response on the Kiddie-SADS-P scale at last assessment. There is no apparent relationship between the two.

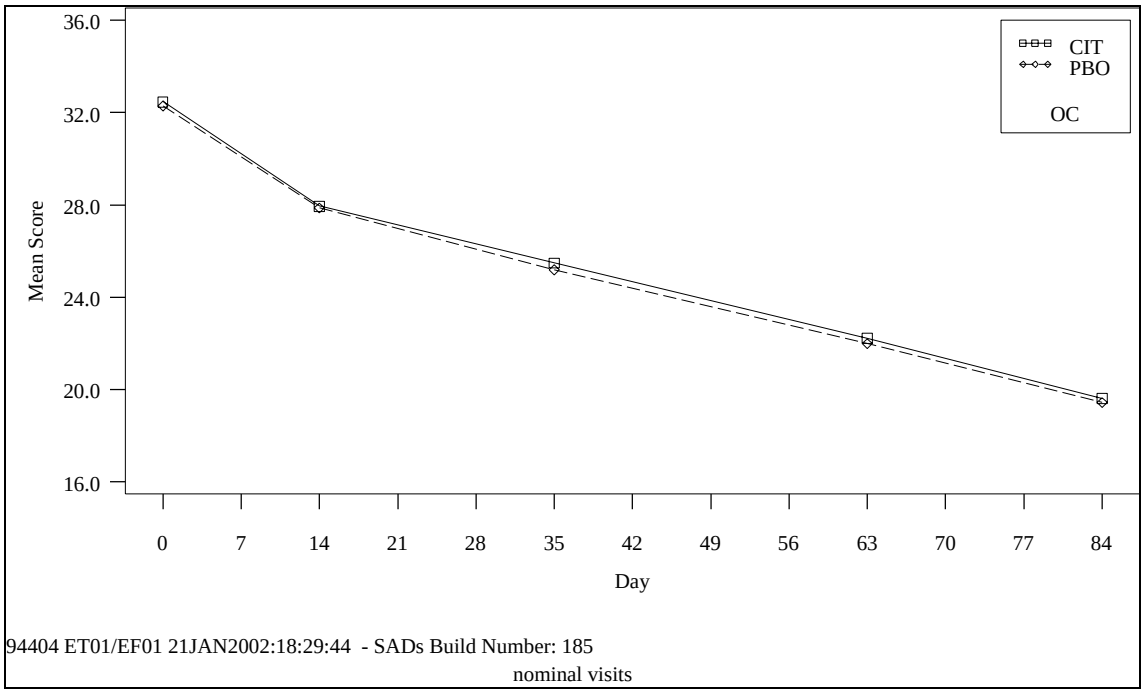
9.3 Primary Efficacy Analysis - Change in Kiddie-SADS-P Total Score over Time

The primary efficacy endpoint was defined as the change from baseline in the Kiddie-SADS-P total score over time (repeated measures). Treatment comparisons were made using the reduced model without the time square factor, since it was not of statistical significance.

The primary analysis failed to detect a statistically significant difference between treatment groups, meaning that a different response profile on the Kiddie-SADS-P scale for citalopram-treated as compared to placebo-treated patients was not established.

In the final reduced model, only baseline Kiddie-SADS-P total score and time were identified as statistically significant factors ($p < 0.001$ for both).

The mean Kiddie-SADS-P total scores over time (OC) are shown in Panel 13 and tabulated by visit in Table 23.



Panel 13 Kiddie-SADS-P Total Scores by Visit Day (OC) (FAS)

Statistical details of the primary efficacy analysis are in Appendix I.9.

Statistical Aspects of the Primary Efficacy Analysis

Centre

Due to inclusion of less than 4 patients in either treatment group into FAS, the following centres were merged into a single collective centre (Centre 100): 02, 05, 24, 26, 27, 28, 31, 32, 34, 35, 42, 44, 45, 51, 54, 55, 71, and 72.

In the model including centre, there was no statistically significant treatment-by-centre interaction; however, there was statistically significant effect of centre ($p = 0.03$). This means that centres did behave differently, but the differences were independent of the treatments given.

Baseline Kiddie-SADS-P Total Score

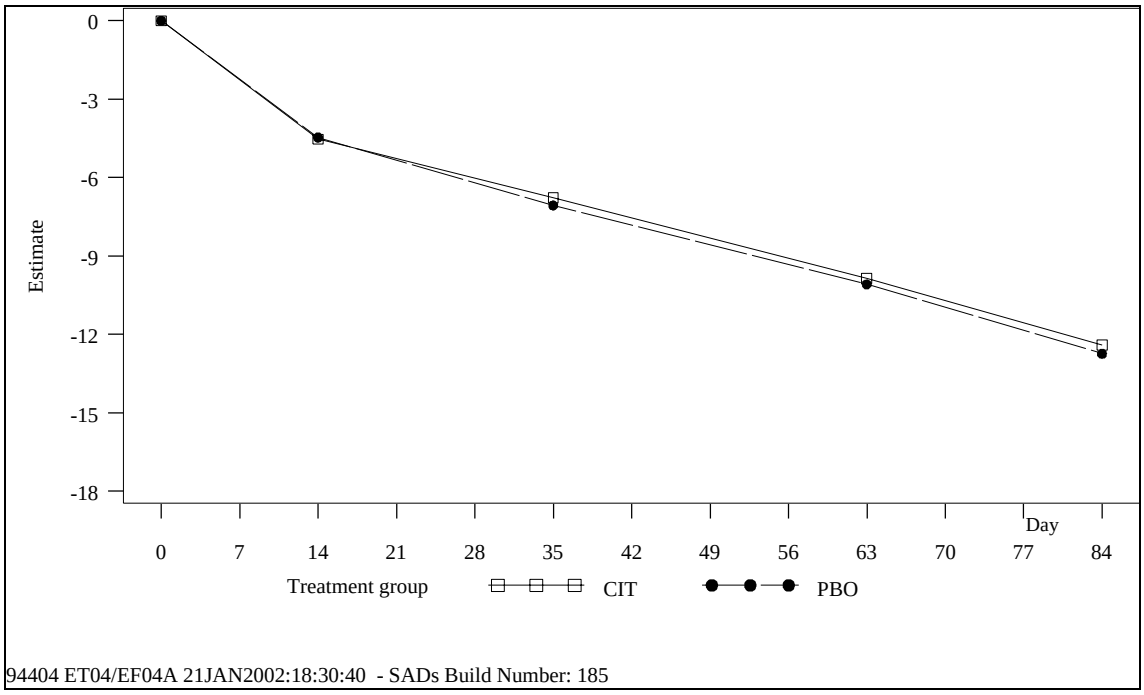
In the main analysis as well as in the model including centre, the baseline Kiddie-SADS-P total score had a statistically significant ($p<0.001$ in both analyses) impact on changes in the Kiddie-SADS-P total score over time. This means that patients with higher baseline Kiddie-SADS-P total scores were likely to show a greater improvement than were patients with lower scores.

9.4 Secondary Efficacy Analyses

9.4.1 Change from Baseline in Kiddie-SADS-P Total Score

The mean Kiddie-SADS-P total scores are tabulated for each visit by OC and LOCF in Table 23 and Table 24**,** respectively, and shown in Panel 13 (OC) and Figure 9 (LOCF).

The adjusted mean changes from baseline in the Kiddie-SADS-P total score are presented graphically in Panel 14 (OC).



Panel 14 Adjusted Mean Changes from Baseline in Kiddie-SADS-P Total Score by Visit Day (FAS)

There were no statistically significant differences between treatment groups in the changes from baseline (adjusted for centre and baseline Kiddie-SADS-P total score) at each visit (Panel 15 and Figure 11) or at last assessment (Panel 16). At Week 12, the adjusted mean reductions were 12.7 and 12.4 points in the placebo and citalopram groups, respectively. The adjusted mean changes from baseline at last assessment in the Kiddie-SADS-P single item scores were not statistically significantly different between treatments (Table 27).

Panel 15 Treatment Differences of the Adjusted Mean Changes from Baseline in Kiddie-SADS-P Total Score by Visit Day (FAS)

Treatment Group	Day @	n	Least Squares Mean	Difference to PBO	SE	95% Confidence Limits Lower	Upper	p-value
PBO	14	107	-4.46					
	35	98	-7.07					
	63	84	-10.09					
	84	77	-12.74					
CIT	14	113	-4.53	-0.07	0.68	-1.41	1.28	0.923
	35	111	-6.77	0.29	0.99	-1.65	2.24	0.765
	63	97	-9.86	0.23	1.18	-2.11	2.56	0.847
	84	83	-12.41	0.33	1.26	-2.16	2.83	0.791

@ nominal visits OC

Model: ANCOVA with treatment and CCentre as factors and baseline score as covariate

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Panel 16 Treatment Difference of the Adjusted Mean Change from Baseline to Last Post-baseline Assessment in Kiddie-SADS-P Total Score (FAS)

Treatment Group	n	Least Squares Mean	Difference to PBO	SE	95% Confidence Limits Lower	Upper	p-value
PBO	108	-9.44					
CIT	115	-9.36	0.07	1.22	-2.33	2.47	0.954

Model: ANCOVA with treatment and CCentre as factors and baseline score as covariate

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For details on the analyses, see Appendix I.9.

9.4.2 Kiddie-SADS-P Response

Response on the Kiddie-SADS-P scale was defined as a score ≤2 on the "depression" and "anhedonia" items. The proportion of patients with response for each treatment group by visit (OC) is shown in Figure 12, Figure 13, and Panel 17.

The proportion of responders increased throughout the study and the placebo response was remarkably high; at Week 12, approximately 60% of the patients in both treatment groups had response on the Kiddie-SADS-P scale. The proportion of patients with response at each visit did not differ between treatment groups.

Panel 17 Differences Between Treatment Groups in the Proportion of Patients with Response on Kiddie-SADS-P by Visit Day (FAS)

		Kiddie-SADS Responders		Estimated Difference	95% Confidence Limits		
Treatment	Day @	n	%	to PBO % points	Lower % points	Upper % points	p-value (Fisher)
PBO	14	13	12.1				
	35	25	25.5				
	63	35	41.7				
	84	47	61.0				
CIT	14	17	15.0	2.9	-6.1	11.9	0.561
	35	29	26.1	0.6	-11.3	12.5	1.000
	63	48	49.5	7.8	-6.7	22.3	0.300
	84	50	60.2	-0.8	-15.9	14.4	1.000

@ nominal visits OC
Response when items 'depression' and 'anhedonia' are scored <= 2

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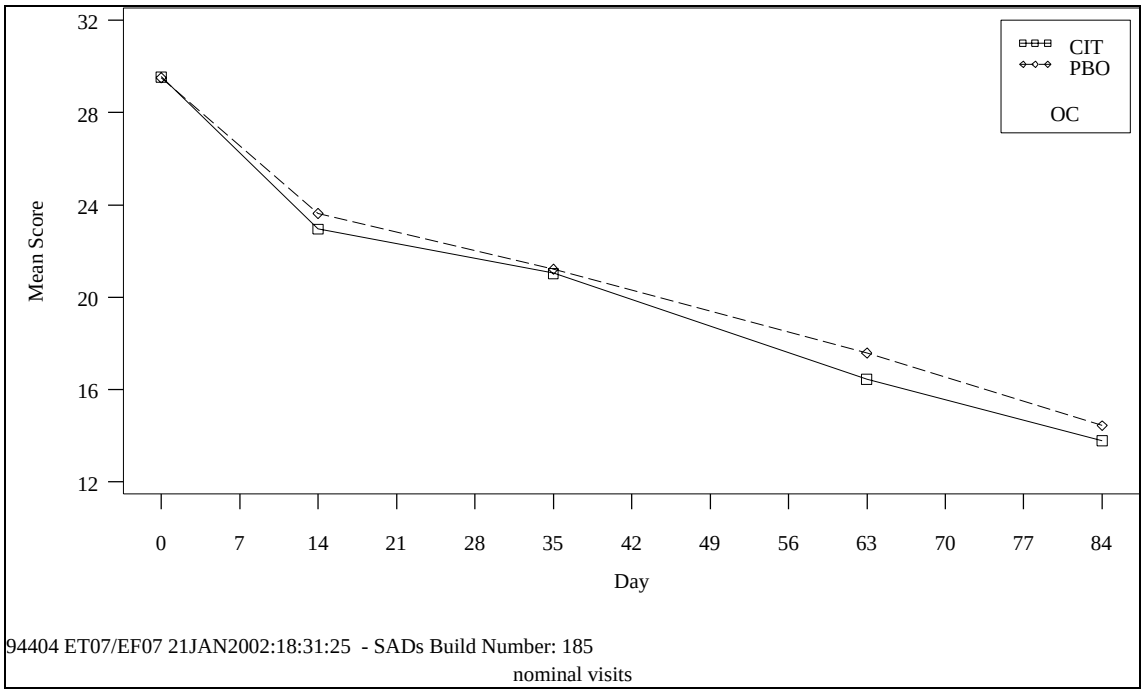
The proportion of patients with response at last assessment (LOCF) is shown in Table 29; 44% of the patients in both treatment groups had response on the Kiddie-SADS-P scale.

For details on the analyses, see Appendix I.9.

9.4.3 Change from Baseline in MADRS Total Score

The mean MADRS total scores are tabulated for each visit by OC and LOCF in Table 30 and Table 31, respectively, and presented graphically in Panel 18 (OC) and Figure 15 (LOCF).



Panel 18 MADRS Total Scores by Visit Day (OC) (FAS)

Repeated Measures Analysis of Change from Baseline in MADRS Total Score

In the repeated measures analysis of change from baseline in MADRS total score (OC) over time, treatment comparisons were made using the reduced model without the time squared factor, since it was not of statistical significance.

The analysis failed to detect a statistically significant difference between treatment groups, meaning that a different response profile on the MADRS scale for citalopram-treated as compared to placebo-treated patients was not established.

In the final reduced model, only baseline MADRS total score and time were identified as statistically significant factors ($p<0.001$).

In the model including centre (centres were merged as in the primary analysis, see section 9.3), neither treatment-by-centre nor centre were factors of statistical significance.

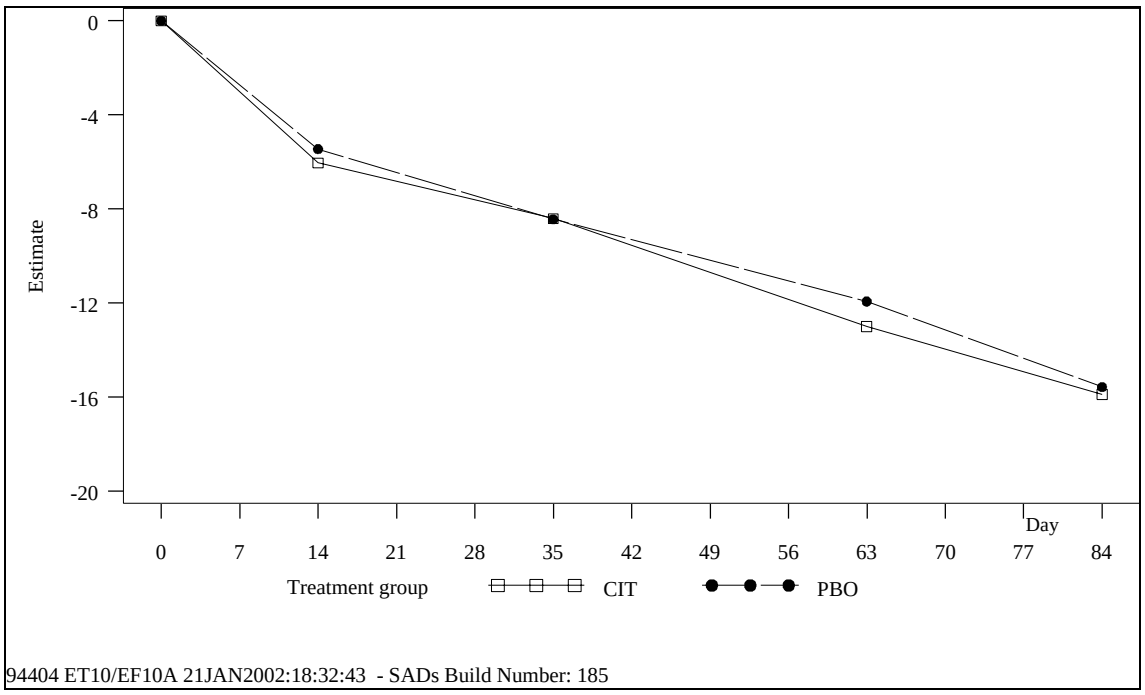
In the main analysis, as well as in the model including centre, the baseline MADRS total score had a statistically significant impact on changes in the MADRS total score over time; in

the main analysis with p<0.001. This means that patients with higher baseline MADRS total scores were likely to show a greater improvement than were patients with lower scores.

Statistical details and output for the analysis are in Appendix I.9.

Change from Baseline in MADRS Total Score by Visit and at Last Assessment

The adjusted mean changes from baseline in the MADRS total score (OC) are presented graphically in Panel 19.



Panel 19 Adjusted Mean Changes from Baseline in MADRS Total Score by Visit Day (FAS)

There were no statistically significant differences between treatment groups in the changes from baseline (adjusted for centre and baseline MADRS total score) at each visit (Panel 20 and Figure 17) or at last assessment (Panel 21). At Week 12, the adjusted mean reductions were 16 points in both treatment groups. The adjusted mean changes from baseline at last assessment in the MADRS single item scores were not statistically significantly different between treatment groups (Table 34).

Panel 20 Treatment Differences of the Adjusted Mean Changes from Baseline in MADRS Total Score by Visit Day (FAS)

Treatment Group	Day @	n	Least Squares Mean	Difference to PBO	SE	95% Confidence Limits Lower	Upper	p-value
PBO	14	90	-5.45					
	35	87	-8.44					
	63	78	-11.93					
	84	70	-15.57					
CIT	14	94	-6.04	-0.59	0.99	-2.55	1.36	0.550
	35	94	-8.40	0.03	1.42	-2.76	2.83	0.982
	63	82	-12.99	-1.06	1.60	-4.23	2.10	0.507
	84	71	-15.88	-0.31	1.68	-3.63	3.01	0.853

@ nominal visits OC

Model: ANCOVA with treatment and CCentre as factors and baseline score as covariate

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Panel 21 Treatment Differences of the Adjusted Mean Change from Baseline to Last Post-baseline Assessment in MADRS Total Score (FAS)

Treatment Group	n	Least Squares Mean	Difference to PBO	SE	95% Confidence Limits Lower	Upper	p-value
PBO	91	-11.91					
CIT	96	-12.09	-0.18	1.67	-3.46	3.11	0.916

Model: ANCOVA with treatment and CCentre as factors and baseline score as covariate

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In the analysis (ANCOVA) of change from baseline to last assessment in MADRS total score, the explanatory variables age, BMI, weight, gender, and centre were included. The inclusion of these parameters did not change the result of the analysis and none of them had a statistically significant impact on the change in MADRS total score.

Statistical details of the analyses are in Appendix I.9.

9.4.4 MADRS Response and Remission

MADRS Response

Response on the MADRS scale was defined as at least a 50% reduction from baseline in the MADRS total score. The proportion of patients with response for each treatment group by visit (OC) is shown in Figure 18, Figure 19, and Panel 22.

Panel 22 Differences Between Treatment Groups in the Proportion of Patients with >=50% Reduction in MADRS Total Score by Visit Day (FAS)

		MADRS >=50% Reduction		Estimated Difference	95% Confidence Limits		
Treatment	Day @	n	%	to PBO % points	Lower % points	Upper % points	p-value (Fisher)
PBO	14	10	11.1				
	35	23	26.4				
	63	31	39.7				
	84	41	58.6				
CIT	14	11	11.7	0.6	-8.6	9.8	1.000
	35	21	22.3	-4.1	-16.6	8.4	0.604
	63	35	42.7	2.9	-12.3	18.2	0.749
	84	43	60.6	2.0	-14.2	18.2	0.865

@ nominal visits OC

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The proportion of responders increased throughout the study period. At Week 12, 59% of patients in the placebo group and 61% of patients in the citalopram group had responded on the MADRS scale. At last assessment, approximately 40% in either treatment group had responded. The proportion of responders did not differ statistically significantly between treatment groups.

The proportion of patients with response at last assessment (LOCF) is shown in Table 36.

Statistical details of the analyses are in Appendix I.9.

MADRS Remission

Remission on the MADRS scale was defined as a MADRS total score ≤12. The proportion of patients with remission for each treatment group by visit (OC) is shown in Panel 23, Figure 20, and Figure 21.

Panel 23 Differences Between Treatment Groups in the Proportion of Patients with MADRS Total Score <= 12 by Visit Day (FAS)

Treatment	Day @	MADRS Remission n	MADRS Remission %	Estimated Difference to PBO % points	95% Confidence Limits Lower % points	95% Confidence Limits Upper % points	p-value (Fisher)
PBO	14	8	8.9				
	35	15	17.2				
	63	25	32.1				
	84	37	52.9				
CIT	14	7	7.4	-1.4	-9.4	6.5	0.792
	35	20	21.3	4.0	-7.4	15.5	0.573
	63	32	39.0	7.0	-7.8	21.8	0.410
	84	36	50.7	-2.2	-18.6	14.3	0.867

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The proportion of patients in remission increased throughout the study period and at Week 12 approximately 50% of the patients in both treatment groups were in remission on the MADRS scale. At last assessment, the proportion of patients with MADRS total score ≤12 was 36% and 33% in the placebo and citalopram groups, respectively. The proportion of patients in remission did not differ statistically significantly between treatment groups.

The proportion of patients in remission at last assessment (LOCF) is shown in Table 38.

Statistical details of the analyses are in Appendix I.9.

9.4.5 BDI

The mean BDI total scores are tabulated for each visit in Table 39 and plotted in Figure 22. Table 40 and Table 41 present data for females and males, respectively, and Figure 23 and Figure 24 are the corresponding graphs.

The adjusted mean changes from baseline in the BDI total score are presented graphically in Figure 25 and Figure 26. Figure 27 and Figure 28 show data on females and Figure 29 and Figure 30 show data on males. Adjusting for centre and baseline BDI total score, the changes from baseline to each visit were not statistically significantly different between treatment groups (Table 42**,** Table 43 (females), and Table 44 (males)). At Week 12, the adjusted mean reduction was 16 points in both treatment groups.

9.4.6 GAF

The GAF mean scores are tabulated by visit in Table 45 and shown graphically in Figure 31. The adjusted mean changes from baseline in GAF mean score are in Figure 32. Treatment differences in the adjusted mean changes from baseline at each visit are presented in Table 46 and Figure 33. No statistically significant differences between treatments were seen. At Week 12, the adjusted mean increase was 18 points in both treatment groups.

9.4.7 Life Event Scale

The LES scores are tabulated by visit in Table 47 and shown in Figure 34. No differences between treatment groups were seen. In both treatment groups, the mean score at baseline was 2.7 points. At week 12, the mean scores were 1.4 points and 1.5 points in the placebo and citalopram groups, respectively.

9.5 Expressed Emotions

FMSS was obtained for 47 patients in the citalopram group and for 41 patients in the placebo group (Table 48). High expressed emotions were assessed in 16 of 76 speech samples with mother and in 1 of 13 speech samples with father.

In a repeated measures analysis, including the same factors as the primary analysis, the results of the speech samples with mother was added as an explanatory variable. Expressed emotions were not found to have a statistically significant impact on the response profile over time.

For documentation of the analysis, see Appendix I.9.

9.6 Efficacy Conclusions

The primary analysis of efficacy could not detect a statistically significantly different response profile on the Kiddie-SADS-P scale over time between placebo and citalopram treatment. In both treatment groups, the mean Kiddie-SADS-P total score decreased as a function of time. In the citalopram group, the adjusted mean reduction in Kiddie-SADS-P total score from baseline to Week 12 (OC) was 12.4 points, a reduction that was not statistically significantly different from that observed in the placebo group (12.7 points). The proportion of responders on the Kiddie-SADS-P scale, defined as patients with score ≤2 on the "depression" and "anhedonia" items, increased during the study. A remarkably high placebo response was observed (61% at Week 12) and the response rate in the citalopram group was similar.

The analyses of scores on the MADRS scale showed similar results. The response profile over time did not differ between treatment groups. The adjusted mean reduction in MADRS total score from baseline to Week 12 (OC) was 16 points in both treatment groups. The proportion

of responders on the MADRS scale, defined as patients with at least a 50% reduction from baseline, increased during the study period. At Week 12, 59% and 61% of the patients treated with placebo and citalopram, respectively, were responders. With respect to frequency of remission, defined as MADRS total score ≤12, no difference between treatments was detected.

The results of the analyses of the BDI and GAF scales did not reveal any additional information regarding the therapeutic effect of citalopram *versus* placebo.

The baseline Kiddie-SADS-P and MADRS total scores had a statistically significant impact on the response profiles over time. This means that patients with higher baseline scores were likely to show a greater improvement than patients with lower scores.

Expressed emotions did not have a statistically significant impact on the response profile over time.

After treatment with 20, 30, and 40 mg citalopram, the mean citalopram serum concentrations at Week 12 were 130, 217, and 288 nmol/L, respectively. No consistent pattern in serum levels in males as compared to females was observed. An apparent relationship between the citalopram serum concentrations and response at last assessment on the Kiddie-SADS-P scale was not detected.

Overall, the proportion of patients withdrawn from the study did not differ between treatment groups. Approximately one-third of the patients withdrew from the study. However, withdrawals due to lack of efficacy were more frequent in the placebo group than in the citalopram group (16% *versus* 9%), whereas withdrawals due to adverse events were slightly more common in the citalopram group (8% in the placebo group and 11% in the citalopram group). The differences were not statistically significant.

12 Conclusions

In this 12-week study, a better therapeutic effect of citalopram in the treatment of adolescent depression as compared to placebo could not be established. The patients showed improvement on the efficacy scales as a function of time, but the placebo response was high and not different from that of citalopram. No impact of expressed emotions on the outcome was identified.

Treatment with citalopram was safe and well tolerated. Safety findings, that were not expected from the safety profile known from adults, were not observed.