7.2.1.2 Study 91206

Investigators/Locations

Principal investigators and study center locations are identified in Appendix 7.2.1.2.

Objectives

The study objective was to demonstrate the safety and efficacy of four doses of citalopram (10, 20, 40, and 60 mg/day) relative to placebo in depressed outpatients.

Population

Participants were outpatients who met DSM-III-R criteria for Major Depression, with the additional requirement that the minimum five symptoms needed for diagnosis had to be present during the same four week period. Also, they were required to have a 21-item HAM-D total score of at least 20 at screening and baseline, including a score of ≥2 on the HAM-D depressed mood item, and show a decrease <20% on the baseline HAM-D score relative to screening. The Raskin Depression Scale score had to exceed the Covi Anxiety Scale score at screening.

Patients had to be in the age range years and women of childbearing potential had to agree to use medically acceptable contraception during the trial and have a negative serum pregnancy test at screening.

Important exclusionary criteria are as follows:

- any other DSM-III or DSM-III-R Axis I condition.
- depression with a seasonal pattern.
- alcohol or substance abuse by DSM-III-R within one year (except nicotine).
- myocardial infarction within one year, implantation of a cardiac pacemaker, or clinically significant cardiovascular disease.
- seizure disorder.
- significant medical condition, to include hypothyroidism, insulin-dependent diabetes, and uncontrolled hypertension.
- any antidepressant within 2 weeks or fluoxetine within 4 weeks of screening.
- ECT within 3 months of screening.
- within the prior three years, lack of response to two antidepressants, one of which was an SSRI, or lack of response to any three antidepressants.
- use of an investigational agent within one month of screening.
- previous investigational use of citalopram.

Design

This was a 12-center, randomized, double-blind, placebo-controlled, fixed dose study consisting of a single-blind, seven day placebo run-in followed by 6 weeks of double-blind treatment. Eligible patients at baseline were randomized to receive one of four fixed doses of citalopram (10, 20, 40, or 60 mg/day) or placebo. Active drug patients in the two highest dose groups (40 and 60mg) were titrated to their assigned dose: all received 20 mg/day on days 1-3 and 40 mg/day on days 4-7; on day 8, the 60mg patients were increased to 60 mg/day. Otherwise, no dose adjustments were permitted. All study medication was taken as a single dose in the evening.

Analysis

The protocol-specified primary efficacy variable is the 21-item HAM-D total score. The efficacy intent-to-treat (ITT) population included all randomized patients who had assessments at baseline and at least one post-baseline assessment. Differences among groups in mean change from baseline score were tested using an analysis of covariance model that included treatment and site as factors and baseline score as the covariate; significant overall F-tests were then further explored using F-tests with the overall mean square error as an error term to contrast each dose group with placebo. Dunnett's procedure was used to adjust for multiple comparisons (i.e., each of the four active drug groups versus placebo), yielding an adjusted α level for statistical significance of 0.014.[6]

Baseline Demographics

Baseline demographic data is displayed in Appendix 7.2.1.2. Randomized groups were not significantly different with respect to gender, age, and race.

Baseline Severity of Illness

Groups did not significantly differ with respect to baseline HAM-D total or depressed mood item scores, MADRS total scores, or CGI severity ratings.

Patient Disposition

A total of 650 patients were randomized to double-blind treatment. The number randomized, the ITT, the completion rate, and the dropout rate due to lack of efficacy for each dose group are summarized in Table 7.2.1.2.1 below.

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[6]David Hoberman, Ph.D., was informally consulted regarding the application of Dunnett's procdure to these data.

Table 7.2.1.2.1: Patient Disposition (Study 91206)					
	Dose Group				
	10mg	20mg	40mg	60mg	Placebo
Randomized (N)	131	130	131	129	129
ITT (N)	123	128	120	110	124
Study Completers [N(%ITT)]	95(77%)	91(71%)	92(77%)	79(72%)	88(71%)
Dropouts D/T Lack of Efficacy [N(%ITT)]	9(7%)	3(2%)	3(3%)	4(4%)	11(9%)

In the 60mg group, about 15% of randomized patients did not qualify for inclusion in the efficacy ITT, a proportion considerably larger than for the other groups. Dropout rates due to lack of efficacy were highest in the placebo and low dose groups.

Concomitant Medications

Concomitant treatment with medication with primarily psychoactive properties was prohibited, except for chloral hydrate which could be used for sleep during run-in and the first week of double-blind treatment.

Forty-seven patients received concomitant medication not permitted by protocol. Only three of these patients received a psychotropic drug: Patient #279 (Cit. 10mg) received a single dose of Librax, Patient #290 (Placebo) received a single dose of flurazepam, and Patient #319 (Cit. 60mg) received one dose of diazepam. These uses of benzodiazepines are unlikely to influence the efficacy results of this study.

Efficacy Results

The primary efficacy variable was the least-squares adjusted mean change from baseline in the HAM-D total score. Additionally, this review focused on changes in the depressed mood item of the HAM-D (item #1), the MADRS total score, and the CGI severity and improvement ratings. Data for these measures, using both the last observation carried forward (LOCF) and observed cases (OC) datasets, are summarized in Appendix 7.2.1.2.

As noted above, an adjusted α level of 0.014, as determined by Dunnett's procedure, was used as the level of critical statistical significance. Thus, the trend range was taken as

$0.014<p\leq0.0500$. Based on this adjusted α, there was statistically significant superiority for citalopram over placebo as indicated in Table 7.2.1.2.2 below.

Table 7.2.1.2.2:
Summary of P-Values for Citalopram/Placebo Comparisons (Study 91206)

Dose Group	Variable	LOCF - Week #						OC - Week #					
		1	2	3	4	5	6	1	2	3	4	5	6
10mg	HAM-D	-	-	-	-	-	-	-	-	-	-	-	-
	HAM-D #1	-	t	-	-	*	*	-	t	-	t	*	*
	MADRS	-	-	-	-	-	-	-	-	-	t	t	t
	CGI-Sev	-	-	-	-	-	-	-	-	-	-	-	-
	CGI-Imp	-	-	-	-	-	-	-	-	-	-	-	-
20mg	HAM-D	-	-	-	-	-	-	-	-	-	-	-	-
	HAM-D #1	-	t	-	-	t	t	-	-	-	-	-	-
	MADRS	-	-	-	-	-	-	-	-	-	-	-	-
	CGI-Sev	-	-	-	-	-	-	-	-	-	-	-	-
	CGI-Imp	-	-	-	-	-	-	-	-	-	-	-	-
40mg	HAM-D	-	-	-	-	t	*	-	-	-	t	-	t
	HAM-D #1	t	t	*	*	*	*	-	t	*	*	*	*
	MADRS	-	-	-	t	*	*	-	-	-	t	*	t
	CGI-Sev	-	-	-	-	-	t	-	-	-	-	-	-
	CGI-Imp	-	-	-	t	*	*	-	-	-	t	t	t
60mg	HAM-D	-	-	-	-	t	*	-	-	-	-	-	-
	HAM-D #1	t	*	*	*	*	*	-	t	*	*	*	*
	MADRS	-	-	-	t	*	*	-	-	-	t	-	t
	CGI-Sev	-	-	-	-	-	-	-	-	-	-	-	-
	CGI-Imp	-	-	-	-	t	*	-	-	-	-	-	-

*= $p\leq0.014$ t=$0.014<p\leq0.0500$ -=$p>0.0500$

There was a progressive decline in HAM-D total scores with time for all treatment groups. For the 10mg group, citalopram was superior to placebo only on the HAM-D depressed mood item, with a

trend toward superiority on the MADRS for the observed cases dataset.

The 20mg group displayed only a trend toward superiority over placebo on the depressed mood item for the LOCF dataset.

Evidence for the 40mg group was considerably stronger. Citalopram beat placebo on the HAM-D and MADRS for LOCF, on the depressed mood item (both LOCF and OC), and on the CGI improvement score for LOCF. Curiously, citalopram failed to beat placebo on the CGI severity item.

For the 60mg group, citalopram was clearly superior to placebo on the depressed mood item (both LOCF and OC); drug also beat placebo on the HAM-D and MADRS total scores and CGI improvement for LOCF. Again, drug did not beat placebo on the CGI severity item.

As mentioned in section 5.4, Richard L. Borison, M.D., Ph.D., the principal investigator for center #2, is under investigation for research fraud. This center contributed 45 (7%) of the 650 randomized patients in this trial.[7] To evaluate the influence of data from this center on the overall efficacy results, the sponsor reanlyzed this study excluding the Borison site and provided the LOCF placebo-adjusted mean change from baseline at week 6 for the HAM-D and the MADRS total scores. The p-values for the overall F-tests were 0.005 (HAM-D) and 0.002 (MADRS); values were identical for parametric and non-parametric analyses. The results of the t-test pairwise comparisons (drug vs. placebo) are summarized in Appendix 7.2.1.2. These data are consistent with the above findings of efficacy for the 40mg and 60mg dose groups.

There did not appear to be a significant treatment-by-center interaction in this study based on the mean change from baseline in HAM-D total score in the LOCF sample for each dose group versus placebo or for all dose groups combined versus placebo at week 6 (α=0.10).

The sponsor proposes to describe in the Clinical Trials of labeling a superiority of citalopram over placebo with respect to certain HAM-D factor subscores (melancholia, psychomotor retardation, and cognitive disturbance). These factors are defined in the ISE as follows:

[7]The breakdown of center #2 patients by treatment group is as follows: 10mg= 10 pts., 20mg= 9 pts., 40mg= 9 pts., 60mg= 9 pts., and placebo= 8 pts.

Factor	HAM-D Items Subsumed by Subfactor
Melancholia	Depressed mood Feelings of guilt Work and activities Retardation Anxiety, psychic Somatic Symptoms, general
Retardation	Depressed mood Work and activities Retardation Genital symptoms
Cognitive Disturbance	Feelings of guilt Suicide Agitation Depersonalization/derealization Paranoid symptoms Obsessive/compulsive symptoms

The retardation and cognitive factors of the HAM-D have been previously described[8] but there is no known documentation to support the melancholia cluster of symptoms as a distinct factor. For these reasons, findings with respect to the melancholia factor should not be described in labeling.

Regarding the retardation and cognitive disturbance factors, Week 6 data are summarized in Appendix 7.2.1.2. At week 6 (LOCF), the 40mg and 60mg groups are superior to placebo on both measures (p-values ≤ 0.0015); the two lower doses did not beat placebo. Visit-wise LOCF data were not provided, but the visit-wise observed cases analysis suggests superiority, with p-values generally in the trend range.

Conclusions

Citalopram demonstrated superiority over placebo at doses of 40 and 60 mg/day. Data for the 10 and 20 mg/day groups did not convincingly demonstrate the efficacy of citalopram over placebo.

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[8]Guy W. ECDEU Assessment Manual for Psychopharmacology. Revised, 1976. U.S. Department of Health, Education, and Welfare.

7.2.1.3 Study 86141

Investigators/Locations

Principal investigators and study center locations are identified in Appendix 7.2.1.3.

Objectives

The objective of this study was to evaluate the antidepressant efficacy and safety of citalopram compared to placebo in elderly depressed patients.

Population

Patients were age 65 and older and required treatment for depression (17-item HAM-D total score ≥14). Exclusion criteria included the following:

- a score >4 for specific impairments in orientation and memory on the Gottfries, Bråne, and Steen dementia rating scale.
- serious heart or lung disease.
- markedly abnormal ECG.
- myocardial infarction within 3 months.
- elevated liver enzymes and bilirubin levels.
- significant renal disease.
- hematological disorders.
- epilepsy.
- psychosis.
- MAOI treatment within 3 weeks.

Design

This was a randomized, double-blind, placebo-controlled, parallel group study conducted at 7 centers. Study entrants underwent a one week, single-blind placebo washout, followed by randomization of eligible patients to six weeks of double-blind treatment with citalopram or placebo in a 2:1 ratio. The citalopram dosing schedule was 10 mg/day for the initial two days, then 20 mg/day; this dose could be reduced to 10 mg/day at any time as a result of adverse effects or increased to 30 mg/day after the first two weeks if there was no therapeutic response. Study medication was given as a single daily dose at about 4:00 PM each afternoon. After four weeks of double-blind treatment, patients not demonstrating an effect were withdrawn from the trial.

Analysis

The efficacy intent-to-treat (ITT) population included all randomized patients who had assessments at baseline and at least one follow-up visit. Between-group differences in mean change from baseline were statistically evaluated using a t-test.

Baseline Demographics

Baseline demographic data is displayed in Appendix 7.2.1.3. The citalopram and placebo groups were comparable with respect to mean age, age range, and gender composition.

Baseline Severity of Illness

There were no statistically significant differences between treatment groups with respect to mean baseline HAM-D total scores, HAM-D depressed mood item scores, MADRS total scores, or CGI-severity scores. About half of the patients in both the citalopram and placebo treatment groups were inpatients. Also, of the patients randomized to each group, 77% of citalopram and 68% of placebo patients had major depression by DSM-III criteria.

Patient Disposition

The study enrolled 181 patients but excluded 32 of these prior to double-blind treatment due to failure to meet inclusion/ exclusion criteria. Of the 149 patients randomized (98 to citalopram and 51 to placebo), two were excluded from the efficacy ITT, one from each group, presumably due to lack of at least one follow-up assessment. The number of completers at weeks 2, 4, and 6 by group is displayed in Appendix 7.2.1.3. Of the ITT samples, 66% of citalopram and 76% of placebo patients completed the study. The proportions of patients who prematurely discontinued due to lack of efficacy and/or deterioration were similar for the citalopram and placebo groups: 23% and 22%, respectively.

Dosing Information

The mean daily dose of citalopram during the study is provided in Appendix 7.2.1.3. For most of the study, the mean dose was in the range

Concomitant Medications

Antidepressant medication other than citalopram was prohibited during the trial. Use of various other psychotropic agents was permitted by protocol, however; the proportions of randomized patients who received the following classes of agents are summarized below:

	Citalopram	Placebo
Antipsychotics	20%	20%
Anxiolytics	27%	27%
Sedative/Hypnotics	35%	41%

Efficacy Results

The four variables considered most important to the demonstration of efficacy are the 17-item HAM-D total score and depressed mood item, MADRS total score, and the CGI-severity score. Results for these measures, using both the last observation carried forward (LOCF) and observed cases (OC) datasets, are summarized in Appendix 7.2.1.3.

There are consistent declines in all four depression measures during double-blind treatment for both the LOCF and OC analyses, for which citalopram is generally numerically superior to placebo. However, the inter-group difference is statistically significant only for OC data at week 6 for the HAM-D total score and the HAM-D depressed mood item; there is a trend favoring citalopram at week 6 for the MADRS total score for OC. For other comparisons, including all LOCF analyses, the p-value is >0.10, or not significant.

Conclusions

The disappointing results from study 86141 may be related to a number of factors, including: 1) a substantial number of patients (27%) who did not meet DSM-III criteria for major depression, contributing to diagnostic heterogeneity and consequent difficulty demonstrating a significant treatment effect, and 2) a relatively low mean citalopram dose (~24 mg/day).

In sum, this study suggests that citalopram may have an antidepressant effect in depressed elderly patients but fails to provide convincing evidence of efficacy in this population.

7.2.1.4 Study 89303

Investigators/Locations

Principal investigators and study center locations are identified in Appendix 7.2.1.4.

Objectives

The objective of this study was to compare the safety and efficacy of two doses of citalopram to placebo in the treatment of patients with moderate to severe depression.

Population

Patients had DSM-III-R major depression, were in the age range 18-70, and had a minimum total score of 22 on the MADRS. The study was open to both inpatients and outpatients. Important exclusionary criteria were:

- clinical or laboratory evidence of serious medical disease.
- ECT within one month.
- MAOI's within two weeks of double-blind treatment.
- fluoxetine within 5 weeks of study entry.
- depressive episode <3 weeks duration.
- organic mental disease.
- history of epilepsy.

Design

This was a randomized, double-blind, placebo-controlled, parallel group, 18-center, fixed dose study. Study entrants underwent a one week, single-blind placebo washout. Then, patients still meeting trial entry criteria were randomized to six weeks of treatment with either citalopram 20 mg/day, citalopram 40 mg/day, or placebo. Patients randomized to the 40mg group received 20 mg/day for the first week and 40 mg/day for the remaining 5 weeks of double-blind treatment. Study medication was given in a single dose each evening between 7:00 and 9:00 PM.

Analysis

The efficacy intent-to-treat (ITT) population included all randomized patients who had assessments at baseline and at least one follow-up evaluation. Differences in mean change from baseline among groups were tested using an analysis of covariance model that included treatment and site as main effects and baseline value as the covariate; significant omnibus tests were then further explored using unpaired t-tests.

Baseline Demographics

Baseline demographic data is displayed in Appendix 7.2.1.4. The citalopram and placebo groups were comparable with respect to mean age, age range, and gender composition.

Baseline Severity of Illness

There were no statistically significant differences between treatment groups with respect to mean baseline HAM-D total scores, HAM-D depressed mood item scores, MADRS total scores, or CGI-severity scores. Overall, 41% of the patients were severely depressed (MADRS≥35, HAM-D≥25), with no significant difference among the groups; the majority of patients were moderately depressed (MADRS 22-34, HAM-D 16-24).

Patient Disposition

Study 89303 enrolled 222 patients into the placebo washout phase; of these, 200 were randomized to receive double-blind treatment (70 to citalopram 20mg, 64 to citalopram 40mg, and 66 to placebo), 22 being dropped due to failure to meet entry criteria

at the end of washout. The number of patients in the efficacy ITT and the number of completers at weeks 1, 3, 4, and 6 by group are displayed in Appendix 7.2.1.4. Of the ITT samples, completion rates were as follows: 75% of citalopram 20mg, 80% of the citalopram 40mg, and 72% of placebo patients. The proportions of efficacy ITT patients who dropped out at least in part because of lack of efficacy were 9%, 6%, and 12% for citalopram 20mg, 40mg, and placebo, respectively.[1]

Concomitant Medications

Sedative/hypnotic use was permitted during this study and, by far, these agents were the most frequently used concomitant medications: 34% of citalopram 20mg, 31% of citalopram 40mg, and 41% of placebo patients used drugs within this class. The only other psychotropic class used was tranquilizers, which were taken by 3%, 5%, and 3% of patients in these groups, respectively.

Efficacy Results

The four variables considered critical to the demonstration of efficacy are the 17-item HAM-D total score, HAM-D depressed mood item, MADRS total score, and the CGI-severity score. Data for these measures, using both the last observation carried forward (LOCF) and observed cases (OC) datasets, are summarized in Appendix 7.2.1.4.

There are consistent declines in all four depression variables during double-blind treatment for both citalopram groups in the LOCF and OC analyses. The citalopram groups are generally numerically superior to placebo from week 3 onward. However, the drug/placebo differences are not consistently statistically significant; p-value data are summarized in Table 7.2.1.4.1 for clarity. Of particular note, there were no significant differences with respect to either the HAM-D or MADRS total scores at weeks 4 and 6, where which one might expect to see a clear drug effect.

Furthermore, these p-values are unadjusted for multiple comparisons related to the use of two active drug arms. If one assumed an Bonferroni adjusted α of 0.025, only two comparisons would be significant (CGI-severity at week 4, observed cases, 20mg vs. placebo; and week 6, LOCF, 40mg vs. placebo).

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[1]Numerators include those dropping out for "lack of efficacy" plus those dropping out for "adverse event & lack of efficacy."

Table 7.2.1.4.1:
Summary of P-Values for Citalopram/Placebo Comparisons (Study 89303)

Dose Group	Variable	LOCF			OC		
		Wk 3	Wk 4	Wk 6	Wk 3	Wk 4	Wk 6
CIT 20	HAM-D	-	-	-	-	t	-
CIT 20	Item 1	-	-	-	-	-	-
CIT 20	MADRS	-	-	-	-	-	-
CIT 20	CGI-S	-	-	t	-	*	t
CIT 40	HAM-D	*	-	-	*	-	-
CIT 40	Item 1	*	t	*	t	-	-
CIT 40	MADRS	*	-	-	t	-	-
CIT 40	CGI-S	t	-	*	t	-	*

*= $p \leq 0.050$ t=$0.050 < p \leq 0.100$ -=$p > 0.100$

Conclusions

It seems that a major contributing factor to the disappointing results of this trial is the large placebo response observed: for instance, at week 6 in the LOCF dataset, placebo patients experienced a decrease in HAM-D total score of 10.56. Other possible factors include the relatively large number of centers, with few patients at each center, and a mix of outpatients and inpatients, both of which may introduce considerable variabilty into the patient samples. Also, small sample sizes were relatively small, with reduced statistical power to detect differences.

In conclusion, Study 89303 fails to provide convincing evidence of an antidepressant effect for citalopram.

7.2.1.5 Study 89306

Investigators/Locations

Principal investigators and study center locations are identified in Appendix 7.2.1.5.

Objectives

The objective of this trial was to compare the safety and efficacy of two fixed doses of citalopram with placebo in the

treatment of patients with moderate to severe depression.

Population

Patients had DSM-III-R major depression, were in the age range 18-70 years, and had a total MADRS score ≥ 22. Both inpatients and outpatients could participate. Important exclusion criteria included:

- clinical or laboratory evidence of serious medical disease.
- ECT within one month.
- MAOI's within two weeks of double-blind treatment.
- fluoxetine within 5 weeks of study entry.
- depressive episode <3 weeks duration.
- organic mental disease.
- history of epilepsy.

Design

This was a randomized, double-blind, placebo-controlled, parallel group, 20-center, fixed dose study. Study entrants underwent a one week, single-blind placebo washout. Then, patients still meeting study entry criteria were randomized to six weeks of treatment with either citalopram 20 mg/day, citalopram 40 mg/day, or placebo. Patients randomized to the 40mg group received 20 mg/day for the first week and 40 mg/day for the remaining 5 weeks of double-blind treatment. Study medication was given in a single dose each evening between 7:00 and 9:00 PM.

Analysis

The efficacy intent-to-treat (ITT) population included all randomized patients who had assessments at baseline and at least one post-baseline assessment. Differences in mean change from baseline among groups were tested using an analysis of covariance model that included treatment and site as main effects and baseline value as the covariate; significant omnibus tests were then further explored using unpaired t-tests.

Baseline Demographics

Baseline demographic data is displayed in Appendix 7.2.1.5. The citalopram and placebo groups were roughly comparable with respect to mean age, age range, and gender composition.

Baseline Severity of Illness

There was no significant difference among treatment groups with respect to the mean CGI severity scores at baseline. There was a trend level difference at baseline between the citalopram 40mg group and placebo with respect to the MADRS total score: mean scores were 31.30 for citalopram 40mg and 33.14 for placebo

(p=0.059). This is unlikely to be of major clinical importance.

Patient Disposition

This trial enrolled 308 patients into the placebo washout phase; at the end of washout, 34 of these failed to meet criteria for entry, leaving 274 to be randomized to receive double-blind treatment (88 to citalopram 20mg, 97 to citalopram 40mg, and 89 to placebo). The number of patients in the efficacy ITT and the number of completers at weeks 1, 3, 4, and 6 by group are displayed in Appendix 7.2.1.5. For patients in the efficacy ITT, completion rates were as follows: 74% of citalopram 20mg, 76% of the citalopram 40mg, and 76% of placebo patients. The proportions of efficacy ITT patients who dropped out at least in part because of lack of efficacy were 10%, 11%, and 7% for citalopram 20mg, 40mg, and placebo, respectively.[2]

Concomitant Medications

The only psychotropic agents permitted during the study were sedative/hypnotics, which were used by 28% of citalopram 20mg, 29% of citalopram 40mg, and 36% of placebo patients during double-blind treatment.

Efficacy Results

The key efficacy variables were the change from baseline in the MADRS total score and in the CGI-severity score; the HAM-D was not assessed in this study. Data for these measures, using both the last observation carried forward (LOCF) and observed cases (OC) datasets, are summarized in Appendix 7.2.1.5.

There were consistent and sizable decreases in both depression variables during double-blind treatment for all three treatment arms in both the LOCF and OC analyses. Owing to the robust mean placebo response, the drug/placebo difference was statistically significant for only one comparison: 20mg vs. placebo, observed cases at week 6 for the MADRS; however, after a Bonferroni adjustment for multiple comparisons due to the two active drug treatment arms, the p-value for this comparison falls only in the trend range.

Conclusions

It appears that the principle reason for the failure of citalopram to show superiority over placebo was the large placebo response, e.g., a mean decrease from baseline of almost 16 points

[2]Numerators include those dropping out for "lack of efficacy/deterioration" plus those dropping out for "adverse event & lack of efficacy."

on the MADRS total at week 6 (LOCF). The basis for this large response is difficult to identify.

In summary, it must be concluded that study 89306 failed to demonstrate convincing therapeutic superiority of citalopram over placebo in the treatment of moderate to severe depression.

7.2.1.6 Study 89304

Investigators/Locations

Principal investigators and center locations are listed in Appendix 7.2.1.6.

Objectives

The objective of this trial was to determine whether patients who responded to short-term treatment for depression with citalopram would experience a continued therapeutic effect in longer-term maintenance therapy (up to 24 additional weeks) compared to responders treated with placebo.

Population

Study participants were patients meeting DSM-III-R criteria for Major Depression who were in the age range . Minimum duration of the current depressive episode was 3 months and minimum MADRS total score was 25. Both inpatients and outpatients could participate. Exclusion criteria included:

- serious renal, hepatic, or cardiovascular disease.
- treatment with MAOI's with 3 months.
- treatment with ECT within 6 months.
- post-partum depression.
- organic mental illness.
- epilepsy.
- previous ineffective treatment with citalopram.
- concomitant treatment with lithium or carbamazepine.

Design

Study 89304 was conducted in two phases (Periods A and B). Period A was an open-label, 31-center study of the effects of citalopram treatment for 8 weeks in patients with Major Depression.

Dosing was begun with citalopram 20 mg/day PO or IV. Oral drug was taken once daily in the evening between 5:00 and 9:00 PM. Parenteral drug was permitted as an intial treatment of inpatients if judged necessary by the investigator. A concentrated solution (40 mg/mL) was diluted in 250 mL of isotonic saline and administered by intravenous infusion over two to three hours; after at most two weeks, patients were continued on an identical oral dose for the remainder of the period. For any patient not showing an effect after one to two weeks, the dose was titrated in increments of 10 to 20 mg/day to a maximum of 60 mg/day. The optimal dose for each patient was established and fixed prior to the end of Period A.

Responders from Period A (i.e. those with a MADRS total score ≤12 at the end of Period A) were then continued for an additional 24 weeks in a randomized, double-blind, placebo-controlled, parallel group study phase (Period B). Period B patients were randomized to either citalopram (at a dose between 20-60 mg/day according to the Period A optimal dose) or placebo, in a ratio of 2:1, respectively. Safety and efficacy assessments were conducted at weeks 4, 8, 12, 16, 20, and 24 during period B (week 8 of period A was considered to be baseline for period B). For Period B citalopram patients, the Period A optimal dose was to be maintained unchanged for the entire Period B.

Analysis

The primary measure of efficacy was defined to be the time to relapse during Period B as assessed by Kaplan Meier analysis and the log rank test to determine the equality of relapse risk between drug and placebo during period B.

Relapse was operationally defined as an increase in MADRS total score to at least 25 PLUS the clinical judgement of relapse by the investigator leading to withdrawal of the patient due to deterioration. Time to relapse was defined as the number of days from the start of Period B double-blind treatment to the date on which the investigator withdrew the patient.

The intent-to-treat (ITT) population for efficacy analyis included all patients with a Period A response to citalopram and who were randomized at the beginning of period B and had a baseline and at least one post-baseline assessment. Data for patients withdrawn for reasons other than relapse or for patients who completed the study were considered as right-censored.

Baseline Demographics

Demographic characteristics of patients at randomization are shown in Appendix 7.2.1.6. The citalopram and placebo groups were roughly comparable with respect to median age, age range, and gender composition.

Baseline Severity of Illness

There was no significant difference between treatment groups[1] with respect to MADRS total scores at entry to Period B (p=0.31).

Patient Disposition

A total of 391 patients received citalopram during period A. Of

[1]Mean MADRS total scores at Period B baseline were 5.2 and 5.8 for citalopram and placebo, respectively.

these, 249 completed Period A and 226 continued treatment in period B; 23 Period A completers did not continue for unspecified reasons. Of the 226 Period A completers who continued treatment, 152 were randomized to citalopram and 74 to placebo. Completing period B treatment were 96 citalopram and 38 placebo patients.

Dosing Information

Mean citalopram dose by visit is displayed in Appendix 7.2.1.6. Although doses were fixed during period B, patients were not randomized to these doses and, thus, this cannot be considered a fixed dose study in the usual sense.

Concomitant Medications

During period B, psychotropic agents of the following three classes were taken by the following proportions of citalopram and placebo patients:

	Citalopram	Placebo
Sedative/Hypnotics	41%	34%
Psycholeptics	4%	1%
Tranquilizers	61%	64%

This use is not felt to appreciably influence the efficacy results of this study.

Efficacy Results

Efficacy results are summarized in Appendix 7.2.1.6. The crude relapse rates were 14% (21/152) in the citalopram group and 24% (18/74) in the placebo group; these rates are significantly different (p=0.044).

The mean (median) time to relapse among those patients relapsing was 21 (12) weeks for citalopram and 18 (12) weekps for placebo.

The Kaplan Meier analysis of time to relapse revealed a statistically significant difference between citalopram and placebo (p=0.04).

With respect to mean HAM-D total scores, both groups displayed deterioration over time, but the placebo group demonstrated greater deterioration on average than citalopram patients:

	Citalopram	Placebo
Baseline	4.7	5.0
Week 24(LOCF)	7.4	9.8
Mean Change	+2.7	+4.8

The drug/placebo difference was not statistically significant.

To evaluate treatment-by-center interaction, the 31 centers in this study were randomly grouped into 14 centers so that there were 14-18 patients per center. An ANOVA was then performed across centers using the drug-placebo difference in mean change from baseline in MADRS total score at final study week (LOCF). This revealed no significant treatment-by-center interaction (p=0.417).

Conclusions

Citalopram was superior to placebo in preventing relapse over a 24 week period in patients who demonstrated an initial response to citalopram.

7.2.1.7 Study 89305

Investigators/Locations

Principal investigators and center locations are listed in Appendix 7.2.1.7.

Objectives

The objective of this study was to compare the safety and efficacy of two doses of citalopram with placebo in the maintenance treatment of moderately to severely depressed patients who have demonstrated a short-term therapeutic response.

Population

The study population consisted of patients from either study 89303 or 89306 who had responded to treatment (MADRS ≤12) in the short-term trial. There were three exclusionary criteria in addition to those applicable for entry into the short-term studies:

- patients who were pregnant or lactating.
- females of childbearing potential not using adequate contraception, in the opinion of the investigator.
- patients with a major depressive episode of more than 12 months duration.

Design

Study 89305 was a randomized, double-blind, placebo-controlled, parallel group, 20-center study which compared 24 weeks of treatment with citalopram 20 mg/day, citalopram 40 mg/day, and placebo in acute responders from the six week studies 89303 and 89306.

Patients in the two short-term studies received either placebo or fixed doses of 20 or 40 mg/day of citalopram. Patients showing a response to either dose of citalopram (i.e., MADRS total score ≤12) were randomized in a 7:3 ratio to either continue their fixed dose of citalopram or receive placebo during study 89305. These patients comprised the three primary efficacy analysis groups: citalopram 20mg→20mg, citalopram 40mg→40mg, and citalopram 20 or 40mg→placebo. Placebo responders from the acute studies were not re-randomized but simply continued on placebo in study 89305; these patients were not part of the primary group for the long-term efficacy analysis.

During study 89305, study medication was administered once daily, each evening between 7:00 and 9:00 PM.

Analysis

The primary measure of efficacy was defined as the time to relapse using Kaplan Meier survival analysis and the log rank test to determine the equality of relapse risk between drug and placebo during maintenance therapy. A Fisher's exact test was used to compare the proportions of patients relapsing between groups.

Relapse was operationally defined as an increase in MADRS total score to at least 22 PLUS the clinical judgement of relapse by the investigator leading to withdrawal of the patient due to deterioration. Time to relapse was defined as the number of days from the start of maintenance treatment to the date on which the investigator withdrew the patient.

The intent-to-treat (ITT) population for efficacy analyis included all patients from studies 89303 and 89306 who responded to citalopram or placebo, were randomized to double-blind treatment in study 89305, had a baseline assessment, and had at least one post-baseline assessment. Data for patients withdrawn for reasons other than relapse or for patients who completed the study were regarded as right-censored.

Baseline Demographics

Demographic characteristics of patients are shown in Appendix 7.2.1.7. The gender ratio among the three primary analysis groups differed slightly, to a degree not statistically significant. Also, there was no statistically significant difference in median age among these three groups and age ranges were comparable.

Baseline Severity of Illness

MADRS total scores at study entry were 5.4, 6.4, and 6.2 for the citalopram 20 and 40mg groups and the citalopram/placebo group,

respectively; these differences were not statistically significant (p=0.77).

Patient Disposition

A total of 207 patients were enrolled in study 89305, of which 147 were citalopram responders from the short-term studies 89303 and 89306; the remaining 60 patients were placebo responders from the acute studies. Of the 147 citalopram responders (the primary analysis group), 48 were randomized to citalopram 20 mg/day, 57 to citalopram 40 mg/day, and 42 to placebo. The number of primary analysis patients in-study by visit is displayed in Appendix 7.2.1.7. Among these patients, completion rates varied somewhat, being highest in the citalopram 40mg group:

	Completion Rate
Citalopram 20 mg/day	54%
Citalopram 40 mg/day	63%
Citalopram/Placebo	45%

Concomitant Medications

Concomitant psychotropic medications were used by the following proportions of primary analysis patients:

	Cit. 20mg	Cit. 40mg	Cit./Placebo
Sedative/Hypnotics	21%	23%	33%
Tranquilizers	2%	0%	2%

Three patients in the citalopram 40mg group were reported to have used a concomitant antidepressant drug during the study; however, the substance actually used was caffeine, which is not widely recognized as an antidepressant drug.

It is unlikely that any of the above concomitant medication use appreciably influenced the efficacy results.

Efficacy Results

Efficacy results are summarized in Appendix 7.2.1.7. The crude relapse rates were 8% (4/48) in the citalopram 20mg group, 12% (7/57) in the citalopram 40mg group, and 31% (13/42) in the placebo group. Differences between each citalopram group and placebo were significant (p=0.006 for 20mg vs. placebo and p=0.022 for 40mg vs. placebo).

The mean (median) time to relapse among those patients relapsing was 16 (12), 15 (12), and 15 (8) weeks for citalopram 20mg, citalopram 40mg, and placebo, respectively.

The Kaplan Meier analysis of relapse hazard revealed a statistically significant difference between citalopram 20mg and placebo (p=0.01) as well as between citalopram 40mg and placebo (p=0.02). The two citalopram groups did not differ (p=0.52).

Additional analysis revealed a center effect for Center #3 (p=0.01, Cox regression analysis): patients from all treatment groups in this center experienced approximately three times the relapse hazard as did patients in other centers.

With respect to mean MADRS total scores, both citalopram dose groups changed little from baseline on average but citalopram patients randomized to placebo experienced appreciable deterioration:

	Cit 20mg	Cit 40mg	Placebo
Baseline	5.4	6.4	6.2
Week 24(LOCF)	6.4	7.8	12.2
Mean Change	+1.0	+1.4	+6.0

To evaluate treatment-by-center interaction, the 19 centers in this study were randomly grouped into 11 centers so that there were 10-26 patients per center. An ANOVA was then performed across centers using the drug-placebo difference in mean change from baseline in MADRS total score at final study week (LOCF). This revealed no significant treatment-by-center interaction for each of the two dose groups (p=0.327 for 20mg vs. placebo and p=0.530 for 40mg vs. placebo).

Conclusions

Citalopram was superior to placebo in reducing the risk of relapse over a 24 week period in patients who demonstrated an short-term response to citalopram.

7.2.2 Other Trials Pertinent to the Evaluation of Efficacy

There are ten other Group I studies of the antidepressant efficacy of citalopram: two short-term, placebo controlled studies; six short-term, active-controlled studies; and two long-term, uncontrolled studies. These trials are briefly described below.

7.2.2.1 Short-Term, Placebo-Controlled Studies

Studies 86A and 87A are short-term, placebo-controlled studies that were prematurely discontinued after enrollment of a relatively small number of patients. Study termination resulted from the IND being placed on clinical hold in July 1985 by the Agency due to dose-related, sudden, unexplained deaths in a chronic dog study. These studies were not presented in detail in the ISE and are not considered to provide pivotal support for the claim of efficacy in depression due to the small number of patients evaluated.

86A: This U.S. study was designed as a four week, randomized, double-blind comparison of four fixed doses of citalopram (10, 20, 40, and 60 mg/day) and placebo in 300 patients with DSM-III major depression or bipolar depression. It was discontinued after enrollment of 24 patients (20 citalopram and 4 placebo patients); only 10 citalopram and 1 placebo patient completed the trial. Efficacy data were not analyzed.

87A: This U.S. study was a six week, double-blind comparison of flexible dose citalopram (20-80 mg/day), imipramine (50-300 mg/day), and placebo in patients hospitalized with DSM-III major depression or bipolar depression. A total of 180 patients were to be studied but only 51 patients (17 per group) had been enrolled when the trial was terminated; 5 citalopram, 4 imipramine, and 4 placebo patients completed the trial. Citalopram patients demonstrated a trend toward superiority over placebo ($p=0.093$) and numerically greater improvement than the imipramine group with respect to mean change from baseline for the 17-item HAM-D (LOCF).

7.2.2.2 Short-Term, Active-Controlled Studies

There are six short-term, active-controlled, studies of the antidepressant efficacy of citalopram. These studies, which cannot produce convincing evidence of efficacy given the absence of a placebo control, are summarized below.

88105: This was a multicenter, randomized, double-blind comparison of flexible doses of citalopram (ranges of 20-30mg/day and 40-60 mg/day) with imipramine (100-150 mg/day) conducted in Scandanavia. A total of 472 depressed patients from general medical practice were studied during double-blind treatment

lasting six weeks. Medication was taken once daily in the evening. The efficacy ITT population (patients with at least one post-baseline assessment) consisted of 451 patients (177 citalopram 20-30mg, 187 citalopram 40-60mg, and 87 imipramine patients); 397 patients completed the study with completion rates of 79% to 86% across the three treatment groups. Average daily doses of citalopram were 25 mg for the low dose group and 48mg for the higher dose group. Mean changes from baseline in the LOCF analysis with respect to the 17-item HAM-D, HAM-D depressed mood item, and CGI-severity score revealed only small, clinically insignificant differences among the three groups.

92302: This multicenter, randomized, double-blind comparison of flexible doses of citalopram (20-40mg/day) with amitriptyline (50-100 mg/day) was conducted in the United Kingdom. A total of 365 elderly patients with major depression were randomized to double-blind treatment lasting eight weeks. Citalopram was taken once daily in the morning; amitriptyline was taken in the evening. The efficacy ITT comprised 360 patients (175 on citalopram and 185 on amitriptyline); 268 patients completed the study with completion rates of 76% and 71% for the citalopram and amitriptyline groups, respectively. Average daily doses of citalopram were about 25mg. Mean changes from baseline in the LOCF analysis with respect to the 17-item HAM-D, HAM-D depressed mood item, MADRS, and CGI-severity score were not significantly different between citalopram and amitriptyline.

89422: This study was conducted as a multicenter, randomized, double-blind comparison of flexible dose citalopram (20-40 mg/day) and fluvoxamine (100-200 mg/day) in the Netherlands. A sum of 217 patients with major depression were randomized to six weeks of double-blind therapy. Citalopram was scheduled to be taken in the evening. Two hundred and three patients made up the efficacy ITT (101 citalopram and 102 fluvoxamine patients); 166 patients completed the study, with completion rates of 80% and 73% for citalopram and fluvoxamine, respectively. The mean citalopram dose was 30 mg/day throughout most of the trial. Mean changes from baseline with respect to the 17-item HAM-D, HAM-D depressed mood item, and CGI-severity score were numerically larger for citalopram than fluvoxamine (LOCF); the change in CGI-severity score favored citalopram over fluvoxamine to a statistically significant degree.

91302: This was a multicenter, randomized, double-blind comparison of fixed doses of citalopram (40 mg/day) and fluoxetine (20 mg/day) in France. Three hundred and sixteen patients with DSM-III-R major depression or bipolar depression were randomized to eight weeks of double-blind therapy. Medication was administered as a single evening dose. The efficacy ITT consisted of 314 patients (158 citalopram and 156 fluoxetine); 250 patients completed the study, with completion rates of 80% and 78% for citalopram and fluoxetine, respectively.

Mean changes from baseline on the 17-item HAM-D, HAM-D depressed mood item, MADRS, and CGI-severity score were comparable for the two treatments (LOCF).

92301: This trial was conducted in France as a multicenter, randomized, double-blind comparison of fixed doses of citalopram (20 mg/day) and fluoxetine (20 mg/day). A total of 357 patients with DSM-III-R major depression were randomized to 8 weeks of double-blind treatment. Medication was administered as a single evening dose. The efficacy ITT comprised 349 patients (171 citalopram and 178 fluoxetine); 315 patients completed this trial, with completion rates being 87% and 89% for citalopram and fluoxetine, respectively. Mean changes from baseline on the 17-item HAM-D, HAM-D depressed mood item, MADRS, and CGI-severity score were comparable for the two treatments (LOCF).

93401: This trial was a multicenter, randomized, double-blind study of flexible doses of citalopram (20-40 mg/day) and mianserin (30-60 mg/day) recently conducted in Europe. Three hundred and thirty-six elderly depressed patients with mild to moderate dementia were enrolled. Further information was not presented as data are being analyzed.

7.2.2.3 Long-Term, Uncontrolled Studies

There are two one-year, uncontrolled trials which likewise cannot provide definitive evidence of the antidepressant efficacy of citalopram.

8213: This was a multicenter, one-year, open-label study of flexible dose citalopram (10-60 mg/day) conducted in Europe. Nine-hundred and ninety-three depressed patients entered the study directly or enrolled after treatment with citalopram in other studies. Most (64%) of the patients had major depression; 15% had dysthymic disorder, with the remainder having a variety of miscellaneous conditions with associated depressed mood. During the first four weeks of treatment, citalopram could be administered either orally or by intravenous infusion;[1] subsequently, medication was given orally as a single evening dose. The most commonly administered maximum doses were 60 mg/day (204 patients), 40 mg/day (162 patients), and 20 mg/day (76 patients). Several patients (29) received maximum doses greater than 60 mg/day. The efficacy ITT comprised 521 patients, with only 162 completing 12 months of treatment. Among completers, the mean change from baseline in the MADRS total score at month 12 was -29.1.

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[1]One hundred and one patients received at least one intravenous dose of citalopram; the basis for this route of administration is unclear.

88A: This study was a U.S., one-year, uncontrolled study of flexible dose citalopram (10-80 mg/day) in 68 patients previously treated with citalopram in other studies. This study was prematurely terminated due to the clinical hold described in section 7.2.2.1. No patients completed 12 months of therapy. Efficacy data were not analyzed.

7.3 Summary of Data Pertinent to Important Clinical Issues

7.3.1 Predictors of Response

Potential interactions between age (<40, 40-60, >60), gender (male vs. female), race (white vs. non-white), and baseline severity of illness (HAM-D <25 vs. ≥25), on the one hand, and efficacy, on the other hand, were evaluated in studies 85A and 91206 by means of formal statistical testing of the LOCF mean change from baseline in the protocol-specified HAM-D total score, HAM-D depressed mood item, and CGI severity score at week 4 (85A) and week 6 (91206), using α=0.10. In study 91206, this was done considering each dose group separately. (Data are found under Tab 3 of the 11/18/97 submission).

There was a statistically significant age-by-treatment interaction in study 85A for the HAM-D total score and HAM-D depressed mood item. In the age group >60, placebo patients experienced a greater mean change from baseline than citalopram patients; in the two younger age groups, the opposite was true. This was also true for the CGI severity score although this difference did not reach statistical significance. However, only 5 placebo and 7 citalopram patients comprised the >60 age group in 85A. In study 91206, this finding was seen only for the HAM-D total score, based on one patient in the 40mg group who experienced a 3 point increase in HAM-D total score at endpoint. Given the limited sample sizes in the oldest subgroup in both studies, these suggestions of an age-by-treatment interaction are difficult to interpret and may not be clinically meaningful.

There was a significant baseline severity-by-treatment interaction in study 91206 based on analyses of changes in the HAM-D depressed mood item and CGI severity score. This finding was not observed in study 85A and was not confirmed by analysis of the HAM-D total score in study 91206. Thus, it likely represents a coincidental finding.

The relationship between serum levels of citalopram and efficacy was investigated by the sponsor by analysis of data from study 91206.[2] Data for all four fixed dose levels of citalopram (10,

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[2]The efficacy of citalopram appears to reside in the (+) enantiomer in in vitro and in vivo studies. The (+) enantiomer of demethylcitalopram has of the activity of the

20, 40, and 60 mg/day) were pooled for purposes of these analyses. Blood samples for citalopram levels were obtained at the last post-baseline visit 10 to 14 hours after the once daily evening dose of citalopram and serum concentrations were measured by HPLC assay.[3]

A linear regression of change from baseline in HAM-D total score on serum cialopram concentration utilizing the LOCF dataset (N=440) showed a correlation coefficient of -0.1162 with a regression line slope that differed from zero to a statistically significant degree (slope=-0.0052, p=0.0147). This is interpreted as no significant correlation between response and citalopram concentration, with a small negative slope that is statistically significant due to the large sample size.

In summary, the above analyses did not provide consistent evidence of an effect of age, gender, race, or baseline severity of illness on antidepressant efficacy. Also, data did not suggest a significant correlation between serum citalopram levels and treatment response.

7.3.2 Size of Treatment Effect

Treatment effect size was examined in terms of the difference between citalopram and placebo with respect to the least-squares adjusted mean change from baseline to endpoint in HAM-D total score (LOCF). Results for study 85A and for the 40mg and 60mg dose groups in study 91206 are displayed in Table 7.3.2 below.

Table 7.3.2:
Treatment Effect Size as Expressed by the LS Mean Change from Baseline to Endpoint in the HAM-D Total Score (LOCF)*

Study	Citalopram	Placebo	Difference
85A	-12.9	-9.6	3.3
91206 (40mg)	-12.2	-9.3	2.9
91206 (60mg)	-12.1		2.8

* Endpoint = week 4 for 85A and week 6 for 91206. Note that the 24-item HAM-D was used in 85A and the 21-item HAM-D in 91206.

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respective parent enantiomer with respect to serotonin reuptake inhibition; the activity of the didemethyl metabolite is lower than that of the demethyl metabolite in in vitro studies.

These drug/placebo differences were all statistically significant (α=0.05 for 85A and 0.014 for 91206). These effect sizes are, however, smaller than those observed with the most recently approved antidepressant drug, mirtazepine (NDA 20,415): in study 003-020, the mean change in the 21-item HAM-D for mirtazepine was -10.3 and for placebo -4.8 (LOCF), yielding a difference of 5.5. Of course, the placebo mean change in the mirtazepine trial was only about half that seen in these studies with citalopram; the mean changes for citalopram were roughly comparable to those for mirtazepine.

Although relatively small, I consider these effect sizes to be clinically meaningful and these data do lend support to the antidepressant claim for citalopram. Based on a comparison of the two dose groups from study 91206, there does not appear to be a dose-response relationship for effect size, despite the suggestion of a concentration-response relationship (see above).

7.3.3 Choice of Dose

Two studies provide support for the approval of citalopram as an antidepressant: study 85A utilized a flexible dose range of 20-80 mg/day, with a mean dose of about 62 mg/day at week 4 among completers; study 91206 studied fixed doses of 10, 20, 40, and 60 mg/day, of which only the 40 and 60mg groups demonstrated convincing evidence of superiority over placebo.

The sponsor proposes a dosing regimen consisting of an initial dose of 20mg once daily. For patients not responding to 20 mg/day, the dose may be increased in 20 mg/day increments, at intervals of at least one week, up to a maximum of 60 mg/day. In the elderly and in patients with hepatic impairment, dosage should not exceed 40 mg/day.

Determination of a reasonable dosing strategy based on available data is not straightforward. The dosing strategy used in study 85A does not permit one to infer the minimum effective citalopram dose since patients were rapidly titrated to their maximum tolerated dose within the first two weeks of the study; it is quite possible that many patients received a higher dose than that necessary to produce a therapeutic response. Among the 48 citalopram patients completing study 85A, the distribution of mean doses for weeks 3 and 4 is as follows:

Mean Daily Dose Range	N
20-40mg	14
41-60mg	6
61-80	28

Thus, over half of these completers were treated with mean doses above the maximum daily dose in proposed by the sponsor (60

mg/day). This distribution raises the possibility that the positive efficacy results might depend heavily on doses higher than recommended.

To explore the possible relationship between dose and efficacy, the sponsor performed a linear regression analysis between the mean change from baseline in HAM-D total score and mean daily dose for these completers. The correlation coefficient was -0.0467 and the slope of the regression line (-0.0210) did not differ significantly from zero (p=0.7662). Based on these data, there was no apparent effect of dose on therapeutic response. Unfortunately, given the forced titration in this study, this finding is not surprising and, of course, does not help in determining an optimal dose range. However, one is still left with the possibility that doses higher than 60 mg/day may be necessary to achieve a satisfactory anitdepressant effect in many patients.

The results of study 91206 support the efficacy of 40 and 60 mg/day doses; on the other hand, while the 10 and 20 mg/day doses failed to convincingly demonstrate efficacy in this study, effectiveness at such lower doses cannot be ruled. Consider for instance study 89305, which provides evidence that 20 mg/day is efficacious in preventing relapse in responders. Granted, it is quite possible that a higher dose is needed to induce remission and that a lower dose effectively maintains remission; but these data do show that 20 mg/day has some pharmacological activity and may be effective as initial treatment.

While it is true that both studies used a starting dose of 20 mg/day, it is not clear whether this dose per se would be effective for some patients. Likewise, it is not known how many patients treated with 60 mg/day with suboptimal results would benefit from a dose increase up to 80 mg/day. In other words, neither the bottom nor the top of the effective dose range are reasonably delineated by these data.

Based on available data, it seems reasonable to recommend a target dose range of 40 to 60 mg/day for most patients. It is suggested that dosing instructions for most patients indicate a starting dose of 20 mg/day, with an increase to 40 mg/day after one week. In view of the typical latency of therapeutic response for antidepressant drugs, 40 mg/day should be continued for 2-4 weeks, after which the dose may be further increased to a maximum of 60 mg/day in patients with suboptimal response to 40 mg/day.

It is recommended that the sponsor conduct an investigation to more clearly define the therapeutic range of citalopram in depressed patients. This may be done post-approval.

7.3.4 Duration of Treatment

Studies 89304 and 89305 randomized citalopram responders to either continued citalopram therapy or placebo for 24 weeks of long-term follow-up. In these cases, roughly half of all efficacy ITT patients completed the trials and both studies provide data considered useful in addressing the duration of treatment.

Study 89304 used doses in the range of 20-60 mg/day (mean dose of 35 mg/day) and study 89305 utilized two fixed citalopram doses, 20 and 40 mg/day. Kaplan Meier survival analyses demonstrated that all three citalopram dose groups were superior to placebo in reducing the risk of relapse during 24 weeks of double-blind treatment. Cumulative relapse rates at 24 weeks are summarized below.

Table 7.3.4:
Long-Term Relapse Prevention Efficacy Results

Study	Percentage Relapse at Wk 24		Kaplan Meier p-value*
	Citalopram	Placebo	
89304	14%	24%	0.04
89305 (20mg)	8%	31%	0.01
89305 (40mg)	12%		0.02

* Citalopram versus placebo.

7.4 Conclusions Regarding Efficacy

The sponsor has provided data from two short-term, adequate, and well-controlled trials (85A and 91206) supporting the effectiveness of citalopram in the treatment of depression. Results are summarized in Appendix 7.4. As discussed in section 7.3.3 above, it seems clear that the target dose range should include 40 to 60 mg/day, although it is less clear whether doses as low as 20 mg/day are effective and whether patients treated with 60 mg/day with suboptimal response would benefit from a dose increase up to 80 mg/day.

Additionally, results from two long-term, relapse prevention studies (89304 and 89305) demonstrate the superiority of citalopram over placebo in reducing the risk of depression relapse for up to 24 weeks.

Three other short-term, placebo-controlled studies (86141, 89303, and 89306) failed to show a consistent, statistically significant advantage of citalopram over placebo. Since none of these studies employed an active comparator agent, assay sensitivity in these patient samples cannot be assessed. However, in two

studies (89303 and 89306), a large placebo response was observed and likely contributed to failed results. In the third study (86141), the effect size for drug, which was unadjusted for a moderate placebo response, was small; this may be related to the low doses used in this study (10-30 mg/day).

In summary, these data are adequate to support the effectiveness claim for citalopram in the treatment of depression and, for treatment responders, in the prevention of relapse for up to 24 weeks.