s22

Summary of Submission and Findings:

Clinical trials

6.3.1 **SOCIAL ANXIETY DISORDER (SAD):** A single randomised trial comparing fixed doses of escitalopram (5, 10 and 20 mg/day), paroxetine (20 mg/day) and placebo in adult patients with SAD over 24 weeks.

6.3.2 **GENERALISED ANXIETY DISORDER (GAD):** The basis of the submission was a meta-analysis of two randomised trials, one flexible dose, direct (head to head), comparison of escitalopram (10-20 mg) and paroxetine (20-50 mg/day) in adult patients with GAD over 24 weeks, and one trial comparing fixed doses of escitalopram (5, 10 and 20 mg/d), paroxetine (20 mg/d) and placebo in adult patients with GAD over 12 weeks.

6.3.3 The trials have been published at the time of submission as follows:

First author	Protocol title	Publication citation
Lader et al (2004)	Efficacy and tolerability of escitalopram in 12- and	Depression and anxiety 2004;

First author	Protocol title	Publication citation
	24-week treatment of social anxiety disorder: randomised double-blind, placebo-controlled, fixed-dose study.	19:241-8.
Bielski et al (2005)	A double-blind comparison of escitalopram and paroxetine in the long-term treatment of generalised anxiety disorder.	Annals of Clinical Psychiatry 2005; 17(2):65-9
Baldwin DS et al (2006)	Escitalopram and paroxetine in the treatment of generalised anxiety disorder.	British Journal of Psychiatry 2006, 189:264-272.

6.3.4 The ESC noted, that although the product information stated that long term treatment is necessary, the duration of the trials was relatively short (12-24 weeks). The TGA delegate originally recommended rejection of escitalopram for GAD on the basis of inadequate demonstration of long-term efficacy. The delegate subsequently evaluated ongoing Study 99769 (not part of the current submission to the PBAC) which was a relapse prevention study in which patients responding after 12 weeks of open-label treatment with escitalopram 10-20mg, were randomized to 24-76 weeks, double- blind treatment to either escitalopram 20mg or placebo.

Results of trials

Comparative effectiveness

6.3.5 The results of the key trials are summarised in the tables below.

SAD: CONFIDENCE INTERVALS FOR DIFFERENCES IN CLINICAL EFFICACY (ESCITALOPRAM 5 MG, 10 AND 20 MG VS PAROXETINE 20 MG (WEEK 24): TRIAL 99270

	ESC 5 vs PAR 20		ESC 10 vs PAR 20		ESC 20 vs PAR 20	
	Estimate	95%CI	Estimate	95%CI	Estimate	95%CI
LSAS total score	1.80	-3.96, 7.56	2.19	-3.73, 8.12	-7.68	-13.43, -1.93
LSAS fear & anxiety	1.07	-1.88, 4.03	1.23	-1.82, 4.28	-3.76	-6.72, -0.81
LSAS avoidance	0.55	-2.47, 3.57	1.03	-2.10, 4.15	-4.10	-7.12, -1.08
CGI-S	0.12	-0.16, 0.41	0.07	-0.22, 0.36	-0.35	-0.63, -0.07
CGI-I	0.00	-0.21, 0.22	0.04	-0.18, 0.26	-0.29	-0.51, -0.08

PBO = placebo; PAR = paroxetine; ESC=escitalopram; LSAS = Liebowitz Socal Anxiety Scale; CGI-S = Global Clinical Impresssion Severity Scale; CGI-I = Global Clinical Impression Improvement Scale

6.3.6 The 95% confidence intervals fall within the post-hoc specified range of -10 to +10 on the LSAS total score (primary efficacy endpoint). Based on these results, the submission claimed that escitalopram 5 mg and 10 mg were of equivalent efficacy to paroxetine 20 mg. Escitalopram 20 mg was claimed to be superior to paroxetine 20mg. However, the PES commentary advised the post-hoc measure of equivalence was considered invalid. Trial 99270 was designed and statistically powered to test the superiority of escitalopram versus placebo in the total LSAS score at week 12 (LOCF). The trial was not designed to estimate equivalence (or non-inferiority). The paroxetine trial arm was included in its lowest recommended dose as an active control. The appropriate design of equivalence trial required that delta (- Δ to +Δ) is determined a priori, to inform a sample size of adequate statistical power to test the non-inferiority hypothesis.

GAD: RESULTS OF META-ANALYSIS OF STUDIES SCT-MD-20 AND 99815 [A]

6.3.7 A meta-analysis was conducted including trial SCT-MD-20 and a subset of patients from trial 99815 who received escitalopram 10mg/d and paroxetine 20mg/d. The results of the meta-analysis are shown in the following table.

	Difference escitalopram vs paroxetine (95% CI)			
Parameter	Week 12	p-value	End of study [b]	p-value

- HAMA total score	2.12 (0.68, 3.56)	0.0040	2.08 (0.62, 3.55)	0.0054
- CGI-S	0.28 (0.06, 0.49)	0.0131	0.31 (0.08, 0.54)	0.0074
- CGI-I	0.33 (0.13, 0.54)	0.0016	0.33 (0.12, 0.55)	0.0024
Responders %				
-Paroxetine	59.9	0.0201	60.9	0.0092
- Escitalopram	70.6		72.7	

HAMA=Hamilton Anxiety Scale, CGI-S = Global Clinical Impresssion Severity Scale; CGI-I = Global Clinical Impression Improvement Scale
a: Includes all patients from study SCT-MD-20 and patients treated with paroxetine and escitalopram 10 mg from study 99815
b: Week 24 for study SCT-MD-20 and week 12 for study 99815

6.3.8 The submission claimed the results show that escitalopram was superior to paroxetine for the treatment of GAD. The PES commentary advised it was not considered valid to claim superiority with the meta-analytic method and results presented.

6.3.9 The ESC advised there was only limited discussion in the submission about what might constitute a clinically important change on the LSAS and HAMA scales. The submission stated that a 10 point difference on the LSAS scale was likely to be clinically significant, but did not provide any further evidence to support this statement.

s22

s22

Summary of Submission and Findings:

Clinical trials

7.2.1 The re-submission presented new trial data as summarised below.

Trial	Treatment	Esc dose	Duration	Details
MD-05	Esc, Pbo	10-20mg/day	8 weeks	Flexible dose
MD-06	Esc, Pbo	10-20mg/day	8 weeks	Flexible dose
MD-07	Esc, Pbo	10-20mg/day	8 weeks	Flexible dose
MD-31	Esc, Pbo	10-20mg/day	8 weeks	Flexible dose
99815 *	Esc 10mg, 20mg, Pbo	10, 20mg/day	12 weeks	Fixed dose
99769	Esc, Pbo	10mg/day	24 weeks	Relapse prevention
MD-17	Esc	10mg/day	24 weeks	Extension study
Hackett	Diazepam, Pbo	15mg/day	8 weeks	Fixed dose

* also in previous submission, includes a paroxetine arm (20mg/day)

7.2.2 Details of the trials published at time of submission are shown below.

Trial/First Author	Publication title	Citation
Escitalopram		
99815 Baldwin DS	Escitalopram and Paroxetine compared to placebo in the treatment of generalized anxiety disorder (GAD).	17th Congress of Neuropsychopharmacology, Sweden, October 2004
99769 Allgulander C	Prevention of relapse in generalized anxiety disorder by escitalopram treatment.	International Journal of Neuropsychopharmacology 2006;9(5):495-5053

Trial/First Author	Publication title	Citation
SCT-MD-17(MD-17) Davidson JRT	Safety and efficacy of escitalopram in the long-term treatment of generalized anxiety disorder	Journal of Clinical Psychiatry 2005;66(11):1441-14465.
Benzodiazepine		
Hackett et al (2003)	A method for controlling for a high placebo response rate in a comparison of venlafaxine XR and diazepam in the short-term treatment of patients with generalised anxiety disorder.	European Psychiatry, 2003. 18(4): 182-187.

s38

Results of trials

Comparative effectiveness

The key results are summarised in the table below:

	Duration	Mean Dose	Mean Δ HAM-A (Esc-Pbo)
Escitalopram			
MD-05	8 wks	12.8mg	-1.6 (-3.2, 0.0)
MD-06	8 wks	12.9mg	-1.48 (-2.83, -0.13)
MD-07	8 wks	12.3mg	-3.49 (-4.93, -2.04)
MD-31	8 wks	15.3mg	-1.52 (-3.28, -0.24)
99815	8 wks	10mg	-2.39 (-4.15, -0.64)
	8 wks	20mg	-1.87 (-3.63, -0.12)
Meta-analysis (8 wks)	χ^2= 5.62	10mg 99815	**-2.19 (-2.93, -1.45)**
	χ^2= 5.40	20mg 99815	**-2.24 (-2.98, -1.49)**
99769 (relapse prevention)	12 wks data	20mg	-5.96 (-7.54, -4.38)
Diazepam	8 wks	15mg	-14.8 diaz; -11.7 pbo; not SS

HAM-A =Hamilton anxiety scale: total score (primary outcome) – mean change from baseline

s38

7.2.5 A summary of the meta-analyses of secondary outcomes at eight weeks (note 99815 was at 12 weeks) are shown below. The relapse prevention study 99769 was not included in the meta-analyses.

Summary of meta-analyses of secondary outcomes

Outcome [a]	n [b]	Chi [2] Hetero	Type [c]	Output	Output (95%CI)
HAM-A<7 remitters [d]	2	0.33	Rand	RR	1.44 (1.10, 1.87)
HAM-A responders [e]	2	0.13	Rand	RR	1.20 (1.03, 1.40)
HAM-A psychic anxiety	5	6.35	Fixed	WMD	-1.62 (-2.05, -1.18)
HAM-A anxiety item	5	7.82	Fixed	WMD	0.31 (-0.41, -0.21)
HAM-A tension item	4	5.45	Fixed	WMD	-0.27 (-0.39, -0.16)
CGI-I	5	2.34	Fixed	WMD	-0.28 (-0.40, -0.17)
CGI-I remitters	5	3.16	Rand	RR	1.31 (1.18, 1.45)

CGI-S	5	4.13	Fixed	WMD	-0.39 (-0.51, -0.27)
HAD anxiety subscale	5	7.65	Fixed	WMD	-1.59 (-2.06, -1.12)
QOL	4	13.23	Fixed	WMD	3.19 (2.04, 4.34)
HAMD	4	1.64	Fixed	WMD	-1.02 (-1.49, -0.55)

CGI–I=Clinical Global Impression – Improvement, CGI–S=Clinical Global Impression – Severity, HAD=Hospital Anxiety and Depression Scale, HAM-A=Hamilton Anxiety Scale, HAMD=Hamilton Depression Scale, QOL=Quality of Life Questionnaire, WMD = weighted mean difference, RR = relative risk

a For dichotomous outcomes, both doses of 99815 included (10mg +20mg), otherwise, only 20mg included in meta-analyses

b number of trials in meta-analyses

c Type of meta-analysis – random or fixed effects

d Remitters: event rates - escitalopram 0.327, placebo 0.227, absolute risk difference = 10%

e Responders: event rates - escitalopram 0.575, placebo 0.465, absolute risk difference=11%

7.2.6 There were significantly improved outcomes in all key secondary efficacy outcomes at 8 weeks, favouring escitalopram.

7.2.7 The HAMD score was not an efficacy endpoint but an assessment of depressive status. While escitalopram was superior to placebo at week 8, the HAMD score ranged from 8.4 to 10.8 at week 8. As a HAMD score of 10-13 indicates mild depression (lower scores mean an absence of depression), all patients were below the HAMD score of 17 (moderate to severe depression) at study entry and endpoint. The re-submission stated that the benefit seen with escitalopram therapy was therefore due to treatment of GAD rather than co-morbid depression.

7.2.8 The following table shows the results of relapse prevention study.

Summary of results relapse prevention study

Trial (Mean dose)	Rx	n/N (%)	Baseline (SD)	Time 1 (SD) [a]	Time 2 (SD) [b]	Mean change T1 (SD)	Mean change T2 (SD)	Diff Esc-Pbo (95%CI) P value
Escitalopram 99769 relapse prevention study								
Open label phase [c]	Esc	187	27.26 (4.15)	8.37 (5.63)	5.74 (3 06)	-18.88 (7.16)	-21.51 (5.51)	NR
	Pbo	188	27.08 (4.69)	7.67 (4.77)	5.07 (3.15)	-19.41 (6.55)	-22.01 (5.96)	
	NonR	116	27.72 (4.39)	18.56 (9.09)	18.94 (9 24)	-9.16 (8.97)	-8.78 (9.17)	
Randomised phase [d]	Esc	186/187 (99)	5.67 (2.88)	7.78 (6.47)	7.80 (7 31)	2.12 (6.54)	2.13 (7.46)	T1 -5.96 (-7 54, -4.38) p<0.001
	Pbo	187/188 (99)	5 02 (3.07)	13.10 (8.72)	13.76 (8 98)	8.08 (8.90)	8.74 (8.95)	T2 -6.61 (-8 28, -4.94) p<0.001

c: In the open label phase the three treatment groups are: Esc = open label phase responders later randomised to esc; Pbo=open label responders later randomised to placebo; NonR=Non-responders in open label phase.

d: 99769 - baseline for double blind phase, difference esc vs placebo was calculated by the re-submission as statistical analyses were not conducted for secondary outcomes.

e: the difference is reported as being statistically non-significant in the article.

NR=not reported

SD standard deviation

7.2.9 In the relapse study (99769), time to relapse was the primary outcome and HAM-A total score was a secondary outcome. Patients received 12 weeks of open-label therapy prior to randomisation to escitalopram or placebo. A significant placebo response was observed in the first 12 week open label period. At the end of 12 weeks, responders (HAM-A<10) were randomly assigned to active drug or placebo for a minimum of 24 weeks additional treatment. In this phase the HAM-A score in the placebo arm changed significantly (from a mean of 5 to 13.8) indicating a worsening of the condition but the HAM-A score in the active arm only changed from 5.7 to 7.8. Similarly, the relapse rate was 19% in the escitalopram arm and 56% rate in the placebo arm, a difference which was statistically significant (Chi-squared test, p<0.001) in favour of escitalopram.

s22

s22

Summary of Submission and Findings:

Clinical trials

7.3.1 The re-submission was based on two new studies 99012 and 99269. The re-submission also provided a meta-analysis for studies 99012 and 99270.

List of trials used in the re-submission

Trial	Treatment	Esc dose	Duration	Details
99270*	Esc 10mg, 20mg, Pbo	10, 20mg/day	24 weeks	Fixed dose
99012	Esc, Pbo	10-20mg/day	12 weeks	Flexible dose
99269	Esc, Pbo	10mg/day	24 weeks	Relapse prevention

*also in previous submission, includes a paroxetine arm (20mg/day)
Esc=escitalopram, pbo=placebo

7.3.2 Details of the trials published at time of submission are shown below.

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
99270 Lader M	Efficacy and tolerability of escitalopram in 12- and 24-week treatment of social anxiety disorder: Randomised, double-blind, placebo-controlled, fixed-dose study.	Depression and Anxiety 2004; 19(4):241-248.
99012 Kasper S	Escitalopram in the treatment of social anxiety disorder: Randomised, placebo-controlled, flexible-dosage study.	British Journal of Psychiatry 2005; 186(MAR.):222-226.
99269 Montgomery SA	A 24-week randomized, double-blind, placebo-controlled study of escitalopram for the prevention of generalized social anxiety disorder.	Journal of Clinical Psychiatry 2005; 66(10):1270-1278.

s38

Result of trials

Comparative effectiveness

7.3.4 The key results are summarised in the table below. The primary outcome of the trials 99270 and 99012 was Liebowitz Social Anxiety Scale which is a scale of 144 points. A clinically important difference is improvement of 10 points according to ECNP consensus meeting March 2003. This was not the primary outcome in 99269 which is time to relapse.

Results of primary outcome: (adjusted mean change in LSAS total score, LOCF) -Escitalopram versus placebo

	99270		99012	99269
	ESC 10mg	**ESC 20mg**	**Escitalopram**	**Escitalopram**
Week 12	-5.07 (-10.32, 0.18)	**-10.31** **(-15.56, -5.06)**	**-7.29** **(-12.37, -2.21)**	-10.97 (-14.70, -7.25)
Week 24	-7.45 (-13.29, -1.62)	-15.09 (-20.92, -9.25))		-12.82 (-16.95, - 8.70)
Meta analysis (Week 12) (99270 & 99012) Using unadjusted change data		**-8.74 (-12.60, -4.89)**		

7.3.5 The mean change in LSAS total score for escitalopram 10mg -5.07(week 12) and -7.45(week 24), escitalopram 20mg dose is -10.31(week 12) and -15.09(week 24) for study 99270, -7.29 for study 99012 and -10.97(week 12) and -12.82(week 24) for study 99269.

7.3.6 The PBAC noted that although the meta-analysis of the primary outcome, adjusted mean change in LSAS mean score, (meta-analysis of studies 99270 & 99012, mean change -8.74 (95% CI -12.60, -4.89) did not meet the clinically significant difference of 10 points at week 12, secondary outcomes at the 24 week time point showed a significantly greater response to therapy (based on significant improvements in % patients with a ≥50% reduction in LSAS, CGI-I, scores, % patients with CGI-I≤2 and CGI-S scores).

7.3.7 The following table provides the results for the secondary outcomes at the 24 week timepoint.

Summary results of secondary efficacy outcomes – Study 99270 and Study 99012

	Study 99270		Study 99012
Outcome	**Escitalopram 10mg**	**Escitalopram 20mg**	
% of patients with >50% reduction in LSAS total score			
Mean % difference (95% CI) esc vs placebo Week 12 Week 24:	 8.7 (-0.6, 18.0) 17.2 (7.0, 27.5)	 18.7 (8.9, 28.4) 27.3 (17.1, 37.6)	NR
Relative Risk* (95% CI) esc vs placebo at: Week 12 Week 24	 1.42 (0.97, 2.08) 1.61 (1.20, 2.15)	 1.91 (1.34, 2.72) 1.96 (1.49, 2.59)	NR
NNT* (95% CI) vs placebo at: Week 12 Week 24	 11 (6, 167) 6 (4, 14)	 5 (4, 11) 4 (3, 6)	NR
% Patients with CGI-I <2			
Difference in % patients with CGI-I <2 esc vs placebo (95% CI) at: Week 12 Week 24	 13.7 (3.0, 24.4) 7.6 (-3.1, 18.4)	 20.8 (10.2, 31.3) 19.6 (9.3, 30.0)	 15.6 (5.3, 25.9) -
Relative Risk* (95% CI) esc vs placebo at: Week 12 Week 24	 1.33 (1.06, 1.67) 1.15 (0.94, 1.41)	 1.50 (1.21, 1.87) 1.39 (1.16, 1.67)	 1.40 (1.12, 1.77) -
NNT* (95% CI) esc vs placebo at: Week 12 Week 24	 7 (4, 33) 13 (5, 32)	 5 (3, 10) 5 (3, 11)	 6 (4, 19) -
Patients with CGI-S<2			
Difference in % patients with CGI-S <2 esc vs placebo (95% CI) at: Week 12 Week 24	 11.1 (2.7, 19.4) 17.8 (8.3, 27.3)	 13.7 (5.1, 22.2) 26.6 (16.9, 36.4)	NR
Relative Risk* (95% CI) esc vs placebo at: Week 12 Week 24	 1.83 (1.14, 2.94) 1.92 (1.33, 2.77)	 2.03 (1.27, 3.22) 2.37 (1.67, 3.38)	NR
NNT* (95% CI) esc vs placebo at: Week 12 Week 24	 9 (5, 37) 6 (4, 12)	 7 (5, 20) 4 (3, 6)	NR

CGI-I = Clinical Global Impression – Improvement, CGI-S= Clinical Global Impression – Severity, esc = escitalopram, LSAS = Liebowitz Social Anxiety Scale, NR = not reported
* calculated value

7.3.8 The results of the primary outcome for Study 99269 are shown below.

Results of primary outcome: Analysis of time to relapse (Study 99269)

Treatment	n / N (%)	No. of relapses	% Relapsed	Mean survival days
Escitalopram	190/190 (100)	42	22.1	135.3
Placebo	181/182 (99.5)	91	50.3	103.5

7.3.9 The results showed twice as many patients in the placebo group relapsed as compared to escitalopram.

s22

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Summary of Submission and Findings:

Scientific basis of comparison:

5.3.1 The key clinical evidence provided was four randomised multi-centre, parallel group, double-blind trials comparing escitalopram (10-20mg) with citalopram (20-40mg) in patients with major depressive disorder (Hamilton depression rating scale [HAMD] >22) over 8 (3 trials) and 24 (1 trial) weeks.

Comparative effectiveness:

5.3.2 The results of the key trials are summarised in the tables below.

Results of the 8-week comparative randomised trials (n=3) for escitalopram (ESC) and citalopram (CIT) versus placebo (PBO) with 95% CI

Outcome - ITT-LOCF	Drug	Study 99003 (N=468) Flexible dose	Study MD01 (N=485) Fixed dose	Study MD02 (N=368) Flexible dose
Primary: MADRS – Difference in mean change from baseline to final assessment	CIT-PBO	-1.48 (-3.30, 0.33) p=0.10	-2.5 (-5.0, -0.1) p=0.041	-1.9 (-4.4, 0.7) p=0.15
	ESC-PBO	-2.91 (-4.73, -1.09) p=0.002	10mg: -3.9 (-6.2, -1.7) p=0.0007 20mg: -4.6 (-6.9, -2.4) p<0.0001	-1.4 (-3.9, 1.0) p=0.25
Secondary: Response Difference in proportion (%) of patients with ≥50% reduction of the MADRS total score from baseline	CIT-PBO	6.2 (-4.9, 17.2) p=0.308		
	ESC-PBO	17.8 (6.8, 28.7) p= 0.002		
Secondary: Remission Difference in proportion (%) of patients with MADRS score ≤12 per complete remission	CIT-PBO	-1.3 (-12.2, 9.6) p=0.82		
	ESC-PBO	9.4 (-1.6, 20.5) p=0.11		
CGI-S – Difference in mean change from baseline to Week 8	CIT-PBO	-0.15 (-0.40, 0.10) p=0.245	-0.3 (-0.6, -0.0) p=0.027	-0.4 (-0.7, -0.0) p=0.024
	ESC-PBO	-0.38 (-0.64, -0.13) p=0.003	10mg: -0.5 (-0.8, -0.3) p=0.0002 20mg: -0.6 (-0.8, -0.3) p<0.0001	-0.1 (-0.4, 0.2) p=0.44
CGI-I – Difference in adjusted change from baseline in CGI-I scores	CIT-PBO	-0.31 (-0.55, -0.06) p=0.014	-0.4 (-0.7, -0.1) p=0.014	-0.4 (-0.6, -0.1) p=0.016
	ESC-PBO	-0.43 (-0.67, -0.18) p=0.001	10mg: -0.5 (-0.8, -0.2) p=0.0007 20mg: -0.6 (-0.8, -0.3) p<0.0001	-0.1 (-0.4, 0.2) p=0.47
CGI-I – Difference in proportion (%) of patients with CGI-I score ≤2	CIT-PBO	10.2 (-0.6, 21.0) p=0.067		
	ESC-PBO	18.4 (7.8, 28.9) p=0.001		
HAMD – Difference in mean change from baseline to Week 8	CIT-PBO		-2.2 (-4.3, -0.0) p=0.052	-2.0 (-4.2, 0.1) p=0.068
	ESC-PBO		10mg: -3.3 (-5.2, -1.3) p=0.0014 20mg: -4.1 (-6.0, -2.1) p<0.0001	-0.7 (-2.8, 1.4) p=0.51
HAMD Depressed mood item – Difference in mean change from baseline to Week 8	CIT-PBO		-0.5 (-0.7, -0.2) p=0.0005	-0.4 (-0.7, -0.0) p=0.024
	ESC-PBO		10mg: -0.5 (-0.7, -0.2) p=0.0006 20mg: -0.5 (-0.8, -0.3) p<0.0001	-0.1 (-0.4, 0.2) p=0.44

LOCF=last observation carried forward

Results of the 24-week Study 99022 for time points during the trial and at the final endpoint for escitalopram (ESC) and citalopram (CIT)

Outcome - ITT-LOCF	Time period	99022 (N=339) Fixed Dose
Primary: MADRS – the development of the total scores using repeated measures analysis on the observed cases (OC) data	Trial	The upper confidence limit for the slope parameter for escitalopram minus the slope parameter for citalopram was 0.12, which is smaller than the 0.375 required for non-inferiority. Escitalopram was thus at least as efficacious as citalopram.
Secondary MADRS – Change from baseline to each assessment in total score	Trial	There were numerically larger improvements for the ESC group than for the CIT group in the LOCF dataset. There were no statistically significant differences between treatment groups in the adjusted mean change from baseline at any time point. (Submission Table 2.6.7)
	Final (Day 168)	CIT -23.44; ESC -23.32 ESC-CIT = 0.12 (95% CI: *-1.02*, 1.25) p=0.84
Response: MADRS – Proportion of patients with ≥50% reduction of the total score from baseline	Trial	There was no statistically significant difference between treatment groups in the proportion of responders at any time point (OC or LOCF). (Submission Table 2.6.8)
	Final (Day 168)	CIT 91.1; ESC 87.6 * *CIT-ESC* = 3.5 (95% CI: -3.7, 10.7) p=0.44
Remission: MADRS – Proportion of patients with a total score ≤12	Trial	There was no statistically significant difference between treatment groups in the proportion of remitters at any time point (OC or LOCF). (Submission Table 2.6.9)
	Final (Day 168)	CIT 82.2; ESC 83.4 * *CIT-ESC* = -1.2 (95% CI: -10.1, 7.6) p=0.88
MADRS – Change from baseline of all single items	Final (Day 168)	For escitalopram, borderline statistical superiority was found for item 10 (suicidal thoughts, p=0.053). In all, eight of the 10 items were numerically superior for escitalopram (items 1, 2, 4, 5, 6, 7, 8, and 10). (Submission Table 2.6.10)
CGI-S – Score/visit	Trial	*No obvious difference between ESC and CIT, but no analysis provided.* (Submission Table 2.6.11)
CGI-S – Change from baseline	Trial	There was no statistically significant difference between treatment groups. (Submission Table 2.6.12)
	Final (Day 168)	CIT -2.57; ESC -2.67 ESC-CIT = -0.10 (95% CI: -0.26, 0.07) *p=0.25*
HAMA scores	Trial	There was no statistically significant difference between treatment groups. (Submission Table 2.6.13)
	Final (Day 168)	CIT -19.70; ESC -19.42 * *CIT-ESC* = -0.29 (95% CI: -0.93, 1.50) p=0.64

** These calulations are actually CIT-ESC, contrary to the other outcomes where ESC-CIT.*
OC=observed cases; LOCF=last observation carried forward

5.3.3 The submission also presented a meta-analysis of the three eight-week trials. Although there was a trend favouring escitalopram over citalopram, the only significant difference in any of the 5 endpoints at 8 weeks was the MADRS score (observed cases).

Pooled analysis of the three 8-week trials

Outcome	ESC vs CIT	OC/LOCF	Mean (95% CI)	p-value
Primary	**MADRS**	OC	**-1.23 (-2.44, -0.02)**	**0.0457**
		LOCF	-1.08 (-2.26, 0.11)	0.0744
Secondary	**CGI-S**	OC	-0.14 (-0.31, 0.02)	0.0790
		LOCF	-0.12 (-0.27, 0.03)	0.1236
	CGI-I	OC	-0.1 (-0.24, 0.05)	0.2048
		LOCF	-0.06 (-0.2, 0.09)	0.4504
	HAMD 17	OC	-0.72 (-1.82, 0.38)	0.1981
		LOCF	-0.64 (-1.67, 0.4)	0.2274
	HAMD 24	OC	-0.78(-2.23, 0.66)	0.2883
		LOCF	-0.67 (-2.02, 0.69)	0.3342

MADRS = Montgomery Asberg Depression Rating Scale; CGI-S/1 = Clinical Global Impression – severity/improvement; HAMD = Hamilton Depression Rating Scale: 17- or 24-item
OC = observed cases; LOCF = last observation carried forward

s22

Search of Internal Company Database for Published Articles and Internal Company Reports

Internal Company Reports on Clinical Efficacy - Key clinical trial reports

Eight clinical trials have been conducted to assess the efficacy and safety of escitalopram compared to citalopram and/or placebo.

Table 2.1. Efficacy studies internal company search – Escitalopram vs citalopram and/- placebo

	Trial ID	***Publications***
Primary Care setting	*99001*	**Excluded** - escitalopram vs. placebo Wade A. Lemming OM. Bang Hedegaard K. Escitalopram 10 mg/day is effective and well tolerated in a placebo-controlled study in depression in primary care. [Journal: Article] International Clinical Psychopharmacology. Vol 17(3) (pp 95-102), 2002. Wade A. Lemming O, Hedegaard. Depression in Primary Care: Escitalopram is efficacious and well tolerated. - In Poster catalogue.
	99003	**Included** Lydiard RB Effects of escitalopram on anxiety symptoms in depression [CONFERENCE ABSTRACT] 2001 Annual Meeting of the American Psychiatric Association; 2001 May 5-10; New Orleans; LA, USA 2001. Montgomery SA, Loft H, and Reines EH Escitalopram 10mg/day: effective antidepressants in primary care patients [CONFERENCE ABSTRACT] 2001 Annual Meeting of the American Psychiatric Association; 2001 May 5-10; New Orleans; LA, USA 2001. Lepola UM, Loft H, and Reines EH Escitalopram: efficacious and well tolerated in depression management in primary care [CONFERENCE ABSTRACT] 2001 Annual Meeting of the American Psychiatric Association; 2001 May 5-10; New Orleans; LA, USA 2001. Gorman J. Comparison of efficacy in placebo-controlled trials of escitalopram and citalopram. [CONFERENCE ABSTRACT] 2001 Annual Meeting of the American Psychiatric Association; 2001 May 5-10; New Orleans; LA, USA 2001.
	99022	**Included** - Unpublished

	99024	Unpublished **excluded** 8 week DB parallel group fixed dose escitalopram vs placebo vs Prozac
	99002	Unpublished **excluded** 12 month open-label escitalopram safety study extension of 99001 and 99003.
Specialist setting	*MD01*	**Included** Burke WJ Fixed-dose study of escitalopram treatment of depression [CONFERENCE ABSTRACT] 2001 Annual Meeting of the American Psychiatric Association; 2001 May 5-10; New Orleans; LA, USA 2001. Burke W Fixed dose study of escitalopram in the treatment of depression 39th Annual Meeting of the American College of Neuropsychopharmacology. 2000; Dec 10-14; San Juan; Puerto Rico 2000. Burke WJ. Gergel I. Bose A. Fixed-dose trial of the single isomer SSRI escitalopram in depressed outpatients. Journal of Clinical Psychiatry. 63(4):331-6, 2002.
	MD02	**Included** Unpublished
	MD03	Unpublished **excluded** Relapse prevention, extension of studies MD01 and MD02 for responders. Escitalopram vs. placebo

2.2 Listing of All Comparative Randomised Trials

The completed randomised controlled trials (RCTs) of escitalopram (Lu 26-054) compared with citalopram are the four clinical trials listed below.

Table 2.2.1 Summary of RCTs presented in this submission

RCTs of escitalopram vs citalopram in treating MDD	
Study ID	*Title of study*
99003	*A double-blind, randomised, placebo-controlled trial evaluating the efficacy and safety of 10mg Lu 26-054 and Citalopram in outpatients with Major Depressive Disorder*
99022	*A double-blind, randomised, comparative trial evaluating the efficacy and safety of a 6-month treatment with Lu 26-054 (10 mg) and citalopram (20 mg) in outpatients with Major Depressive Disorder.*
MD01	*Fixed dose comparison of the safety and efficacy of Lu 26-054, Citalopram and placebo in the treatment of Major Depressive Disorder.*
MD02	*Flexible dose comparison of the safety and efficacy of Lu 26-054, Citalopram, and placebo in the treatment of Major Depressive Disorder.*

Lundbeck have supplied the reports of these trials, Study Ids 99003, 99022, MD01 and MD02. These are attached as Appendix 4 to Appendix 7 along with the Clinical Expert Report (Appendix 8) and current prescribing Information (Appendix 2).

2.3 Selection of All Comparative Randomised Trials

All RCTs listed in Table 2.2.1 have been included in this analysis.

2.4 Assessment of the Measures Taken by Investigators to Minimise Bias in the Comparative Randomised Trials.

Tables 2.4.1-2.4.4 detail the measures used to minimise bias for each of the trials listed in Table 2.2.1.

All trials were randomised, multi-centre, parallel group, and double-blinded. The randomisation code was not broken for any patient during any of the studies.

Randomisation and dosage

In each trial randomisation was performed using a computer generated randomisation schedule.

In trial 99003, patients were assigned a screening number at the screening visit, in the range from S5001 to S6917 for all countries, except Sweden, where due to labelling requirements screening numbers were from S6918 to S7025. H.Lundbeck A/S generated the screening code.

Patients who did not meet the selection criteria at the baseline visit were assigned a screening failure number (in practice, F plus their screening number). Patients who met the selection criteria at the screening and baseline visits were assigned to treatment in a 1:1:1 ratio of escitalopram to citalopram to placebo (randomisation in blocks of six) according to a randomisation code generated by H.Lundbeck A/S.

Randomisation numbers and study product were prepared for a total of 1350 patients for three treatments (450 patients on each treatment) using numbers R3001 to R4350. Some of these randomisation numbers were allocated separately for Sweden, which used numbers from R4279 to R4302. At each study centre, patients were to be consecutively assigned the lowest randomisation number available.

In trial 99022, patients were assigned a screening number in the range from S2001 to S4100 according to a screening code generated by H.Lundbeck A/S.

Patients who did not meet the selection criteria at the baseline visit were assigned a screening failure number (in practice, F plus their screening number). Patients who met the selection criteria at the screening and baseline visits were assigned to treatment in a 1:1 ratio of escitalopram to citalopram according to a randomisation code generated by H.Lundbeck A/S.

Randomisation numbers and study product were prepared for a total of 1050 patients (525 patients on each treatment) using numbers R7001 to R8050. At each study centre, patients were to be consecutively assigned the lowest randomisation number available.

In studies MD01 and MD02, a list of patient randomisation numbers and the corresponding assigned treatment was generated by the Forest Laboratories Department of Biostatistics. Each study site was provided with drug supplies corresponding to a sequence of patient numbers. The first patient to enter into the study was assigned the first number in the sequence, and each subsequent patient entered was assigned a sequential patient number.

Patients who met all eligibility criteria at screening were dispensed one bottle containing 10 placebo capsules for the one-week, single-blind lead-in and were instructed to take one capsule every evening.

In Study MD01, at the end of the lead-in period, all patients who continued to meet the entrance criteria were assigned a randomisation number and dispensed the corresponding bottle of double-blind study medication for Week 1. Patients randomised to the placebo or 10 mg/day escitalopram groups started double-blind treatment at their assigned dose level, whereas patients randomised to the 20 mg/day escitalopram or 40 mg/day citalopram groups were titrated to their assigned dose level. Thus, during the first week of double-blind treatment, placebo patients took one placebo capsule daily, escitalopram patients took one 10 mg escitalopram capsule daily, 20 mg/day escitalopram patients took one 10 mg escitalopram capsule daily, and 40 mg/day citalopram patients took one 20 mg citalopram capsule daily. Patients were to begin dosing on the evening of the baseline visit (the day study medication was dispensed), although dosing could be switched to the morning, if preferred.

At the end of Week 1, patients were dispensed a new bottle of double-blind study medication and continued taking one capsule daily, with all patients receiving their assigned dose. Thus, placebo patients took one placebo capsule daily, 10 mg/day escitalopram patients took one 10 mg escitalopram capsule daily, 20 mg/day escitalopram patients took one 20 mg escitalopram capsule daily, and 40 mg/day citalopram patients took one 40 mg citalopram capsule daily. At the end of Weeks 2, 4, and 6, patients were dispensed two bottles (one bottle for each week of the study) of their double-blind study medication and continued taking one capsule daily.

In study MD02, patients were to begin dosing (either one capsule of 10 mg escitalopram, one capsule of 20 mg citalopram, or one placebo capsule) on the evening of the baseline visit (the day study medication was dispensed). At the end of weeks 1 and 2, patients were dispensed one bottle of double-blind medication and continued taking one capsule daily.

In the absence of dose-limiting adverse events, dosage could be increased at the end of week 3 or at subsequent visits if, in the investigator's opinion, a satisfactory therapeutic response had not been obtained. Such patients were dispensed two bottles of double-blind study medication and instructed to take two capsules once daily.

Dosage could be decreased at any time because of adverse events. The minimum dose permitted was one capsule per day (10 mg/day escitalopram, 20 mg/day citalopram, or placebo). The maximum dose permitted was two capsules per day (20 mg/day escitalopram, 40 mg/day citalopram, or placebo).

Blinding

In study 99003, the three sets of sealed envelopes containing coded details for each patient in the double-blind treatment phase were prepared. One copy was kept by each of the following: the International Clinical Research-Mood Disorder Department at H.Lundbeck A/S, the Division of International Safety and Pharmacovigilance (ISPV) at H.Lundbeck A/S, and the investigator or pharmacist. All envelopes were collected at the end of the study.

Escitalopram, citalopram, and placebo treatments were visually indistinguishable from one another since the tablets were identical in appearance and shape. Wallet

cards were labelled with a screening number (run-in phase) or a randomisation number (double-blind phase). The screening product was packed in wallet cards containing 10 tablets. For the double-blind phase, tablets were packed into wallet cards containing treatment for 1-week. Two types of wallet cards were packed: one type contained 10 tablets, corresponding to 1 tablet daily for 1-week with 3 extra days, and the other wallet card contained 20 tablets, corresponding to 2 tablets daily for 1-week with 3 extra days. Wallet cards containing 10 tablets were used for Visits 2, 3, 4, and 5, while wallet cards containing 20 tablets could be used for Visits 6 and 7 (if the dosage had been increased).

The randomisation code was to be broken only in an emergency situation in order to give the patient optimal treatment. If possible, the investigator was to consult the study director or monitor before code break. After code break the monitor was to be notified immediately, and the patient withdrawn from the study. The randomisation code was not broken for any patient during the study.

In study 99022, three sets of sealed envelopes containing coded details for each patient in the double-blind treatment phase were prepared. One copy was kept by each of the following: International Clinical Research at Lundbeck France, the Division of International Safety and Pharmacovigilance (ISPV) at H. Lundbeck A/S, and the investigator or pharmacist. All envelopes were collected at the end of the study.

In study 99022, escitalopram and citalopram were visually indistinguishable from one another since the tablets were identical in appearance and shape. Tablets were packed into plastic bottles (tamper-evident Duma containers) and labelled appropriately. The randomisation code was to be broken only in an emergency situation in order to give the patient optimal treatment. If possible, the investigator was to consult the study director or monitor before code break. After code break the monitor was to be notified immediately, and the patient withdrawn from the study. The randomisation code was broken for one patient during the study.

In studies MD01 and MD02, identically appearing bottles of double-blind medication were labelled with a two-part, three-panel label. The first panel remained on the bottle at dispensing and the second and third panels were torn at the perforation and placed in the patient's CRF. If opened, the third panel would reveal the treatment corresponding to the patient randomisation number on the label. No double-blind treatment assignment was unblinded by this procedure or by any other procedure before database lock in either trial.

Follow-up

In study 99003, the withdrawal rate was very low (7%). There was no significant difference in the withdrawal rates between escitalopram (6%), placebo (10%), and citalopram (5%).

In study MD01, 76% of patients completed treatment. The withdrawal rate was similar for all groups with the rate for escitalopram being numerically lower than for citalopram or PBO. The rates were 20.2% for escitalopram (ESC) 10mg, 24.8% for ESC 20mg and 25.6% for citalopram and 25.4% for PBO. The number of patients withdrawing due to adverse event were 4.2% for ESC 10mg, 10.4% for ESC 20mg and 8.8% for citalopram 40mg and 2.5% for PBO. The rates are similar for the higher dose of escitalopram and citalopram and low for the recommended dose of 10mg of escitalopram. These results indicate that escitalopram is well tolerated.

Study MD02 had an overall completion rate of 80% with the results broadly similar for each treatment group (76.8% for ESC 10-20mg, 80.5% for citalopram 20-40mg and 82.7% for PBO). The withdrawal rates for adverse events were similar to Study MD01 (8.8% for ESC 10-20mg, 4.1% for citalopram 20-40mg and 3.1% for PBO), confirming that escitalopram is well tolerated.

Study number 99022 was the longest study, 25 weeks compared with the other three which were eight weeks long. The completion rate was 78.2%, similar to MD01 and MD02 with more patients in the escitalopram arm completing the study (78.2%) compared with those on citalopram (74.2%). The withdrawal rates for adverse events were lower for escitalopram (9.9% for ESC 10mg, 5.7% for citalopram 20mg), further confirming the tolerability of escitalopram.

Table 2.4.1 Procedures for minimising bias for Study No 99003

	STUDY No 99003 Flexible dose – primary care			
Randomisation	*Randomised multi-centre, parallel-group, PBO controlled trial* *Randomisation by means of a computer generated randomisation schedule, with patients at each centre assigned in an ascending sequence.*			
Adequacy of follow-up	*A total of 471 patients were randomised into the study (APRS). 2 randomised patients withdrew their consent to participate before taking any double-blind study product. Thus the All Patients Treated Set (APTS) was 469.*			
	PBO (%)	*CIT 20-40mg (%)*	*ESC 10-20mg (%)*	*TOTAL (%)*
Number randomised to treatment (APRS)	*154*	*161*	*156*	*471*
Patients treated (APTS)	*154*	*160*	*155*	*469*
Full analysis set (FAS) = ITT	*154*	*159*	*155*	*468*
Patients completed	*139 (90.3)*	*152 (95.0)*	*146 (94.2)*	*437 (93.2)*
Patients withdrawn	*15 (9.7)*	*8(5.0)*	*9 (5.8)*	*32 (6.8)*
Primary reason for withdrawal				
Adverse event(s)	*4 (2.6)*	*6 (3.8)*	*4 (2.6)*	*14 (3.0)*
Lack of efficacy	*5 (3.2)*	*1 (0.6)*	*0 (0.0)*	*6 (1.3)*
Per protocol Set (PPS)	*144*	*151*	*146*	*441*
Blinding of outcomes	*Active and placebo tablets were identical, and were packed in identical wallet cards containing 10 or 20 tablets, corresponding to the single daily tablet dose or double daily tablet dose as required. Sealed envelopes containing coded treatment details for each patient were prepared in case of an emergency, but the randomisation code was not broken for any patient during the study.*			

APRS: All Patients Randomised Set – all patients randomised in the study.

APTS: All patients Treated set – all randomised patients who took at least one dose of double-blind study product.

PPS: Per Protocol Set

FAS – all randomised patients who took at least one dose of double blind study product and who had at least one post-baseline assessment of the MADRS total score.

ITT: Intention to Treat – equivalent to FAS

Table 2.4.2 Procedures for minimising bias for Study No 99022

	STUDY No 99022 Fixed dose – primary care		
Randomisation	*Multinational, randomised, double-blind, parallel-group, active controlled trial. Randomisation by means of a computer generated randomisation schedule, with patients at each centre assigned in an ascending sequence.*		
Adequacy of follow-up	*A total of 357 patients were randomised into the study (APRS). All patients started treatment. Thus the All Patients Treated Set (APTS) was 357.*		
	CIT 20mg (%)	*ESC 10mg (%)*	*TOTAL (%)*
Number randomised to treatment (APRS)	*182*	*175*	*357*
Patients treated (APTS)	*182*	*175*	*357*
Full analysis set (FAS) = ITT	*174*	*165*	*339*
Patients completed	*135 (74.2)*	*144 (82.3)*	*279 (78.2)*
Patients withdrawn from APTS	*47 (25.8)*	*31 (17.7)*	*78 (21.8)*
Primary reason for withdrawal			
Adverse event(s)	*18 (9.9)*	*10 (5.7)*	*28 (7.8)*
Lack of efficacy	*3 (1.6)*	*2 (1.1)*	*5 (1.4)*
Non-compliance with study product	*0 (0)*	*2 (1.1)*	*2 (0.6)*
Protocol violation	*8 (4.4)*	*4 (2.3)*	*12 (3.4)*
Withdrawal of consent	*3 (1.6)*	*0 (0)*	*3 (0.8)*
Lost to follow up	*2 (1.1)*	*0 (0)*	*2 (0.6)*
Administrative or other reasons	*13 (7.1)*	*13 (7.4)*	*26 (7.3)*
Per protocol Set (PPS)	*145*	*141*	*286*
Blinding of outcomes	*Escitalopram and citalopram tablets were identical, and were packed in into plastic bottles (tamper-evident Duma containers) and labelled appropriately. Sealed envelopes containing coded treatment details for each patient were prepared in case of an emergency. The randomisation code was broken for one patient during the study.*		

APRS: All Patients Randomised Set – all patients randomised in the study.

APTS: All patients Treated set – all randomised patients who took at least one dose of double-blind study product.

PPS: Per Protocol Set

FAS – all randomised patients who took at least one dose of double blind study product and who had at least one post-baseline assessment of the MADRS total score.

ITT: Intention to Treat – equivalent to FAS

Table 2.4.3 Procedures for minimising bias for Study No MD01

	STUDY No MD01 Fixed dose – specialist care				
Randomisation	*Randomised, parallel-group, PBO controlled trials* *Randomisation by means of a computer generated randomisation schedule, with patients at each centre assigned in an ascending sequence.*				
Adequacy of follow-up	*All patients randomised to treatment were included in the intent-to-treat analysis. A total of 373 of 491 (76.0%) of randomised patients completed the study, with similar proportions of patients completing in each treatment group.*				
	ESC 10mg (%)	*ESC 20mg (%)*	*CIT 40mg (%)*	*PBO (%)*	*TOTAL (%)*
Number randomised to treatment (APRS)	*124*	*128*	*127*	*127*	*506*
Did not receive study drug	*5*	*3*	*2*	*5*	*15*
Patients treated (APTS)	*119*	*125*	*125*	*122*	*491*
Intention to treat (ITT)	*118 (99.2)*	*123 (98.4)*	*125 (100.0)*	*119 (97.5)*	*485 (98.8)*
Patients withdrawn	*24 (20.2)*	*31(24.8)*	*32 (25.6)*	*31(25.4)*	*118 (24.0)*
Patients completed	*95 (79.8)*	*94 (75.2)*	*93 (74.4)*	*91 (74.6)*	*373 (76.0)*
*Primary reason for withdrawal**					
Adverse Event	*5 (4.2%)*	*13 (10.4%)*	*11 (8.8%)*	*3 (2.5%)*	*32 (6.5%)*
Insufficient Therapeutic Response	*3 (2.5%)*	*0*	*1 (0.8%)*	*6 (4.9%)*	*10 (2.0%)*
Withdrawal of Consent	*2 (1.7%)*	*6 (4.8%)*	*3 (2.4%)*	*10 (8.2%)*	*21 (4.3%)*
Lost to follow-up	*11 (9.2%)*	*8 (6.4%)*	*15 (12.0%)*	*10 (8.2%)*	*44 (9.0%)*
Protocol Violation	*3 (2.5%)*	*3 (2.4%)*	*1 (0.8%)*	*1 (0.8%)*	*8 (1.6%)*
Other	*0*	*1 (0.8%)*	*1 (0.8%)*	*1 (0.8%)*	*3 (0.6%)*
Blinding of outcomes	*For the double-blind treatment, patients were supplied medication in the form of encapsulated tablets. All encapsulated medication appeared identical, and was packed in identical bottles of 10 capsules. Where the dose was escalated, two bottles of medication were dispensed.* *The treatment code for each patient was concealed in a panel of each bottle label which was attached to the patient CRF at dispensing, and which could be opened in case of emergency. The randomisation code was not broken for any patient prior to database lock.*				

APRS: All Patients Randomised Set – all patients randomised in the study.

APTS: All patients Treated set – all randomised patients who took at least one dose of double-blind study product.

ITT: Intention to Treat – all randomised patients who took at least one dose of double blind study product and who had at least one post-baseline assessment of the MADRS total score.

** Percentages are relative to number of patients (N) in APTS population.*

Table 2.4.4 Procedures for minimising bias for Study No MD02

	STUDY No MD02 Flexible dose – primary care			
Randomisation	*Randomised, parallel-group, PBO controlled trials* *Randomisation by means of a computer generated randomisation schedule, with patients at each centre assigned in an ascending sequence.*			
Adequacy of follow-up	*All patients randomised to treatment were included in the intent-to-treat analysis. A total of 300 of 375 (80.0%) of randomised patients completed the study, with similar proportions of patients completing in each treatment group. (77% of escitalopram treated patients, 80% of citalopram patients and 83% of placebo patients).*			
	ESC 10-20mg (%)	*CIT 20-40mg (%)*	*PBO (%)*	*TOTAL %)*
Number randomised to treatment (APRS)	*129*	*128*	*129*	*386*
Did not receive study drug	*4*	*5*	*2*	*11*
Patients treated (APTS)	*125*	*123*	*127*	*375*
Intention to treat (ITT)	*124*	*119*	*125*	*368*
Patients completed	*96 (76.8%)*	*99 (80.5%)*	*105 (82.7%)*	*300 (80.0%)*
Patients withdrawn	*29 (23.2%)*	*24 (19.5%)*	*22 (17.3%)*	*75 (20.0%)*
Adverse Event	*11 (8.8%)*	*5 (4.1%)*	*4 (3.1%)*	*20 (5.3%)*
Insufficient Therapeutic Response	*2 (1.6%)*	*1 (0.8%)*	*1 (0.8%)*	*4 (1.1%)*
Withdrawal of Consent	*5 (4.0%)*	*6 (4.9%)*	*6 (4.7%)*	*17 (4.5%)*
Lost to follow-up	*7 (5.6%)*	*10 (8.1%)*	*6 (4.7%)*	*23 (6.1%)*
Protocol Violation	*3 (2.4%)*	*2 (1.6%)*	*3 (2.4%)*	*8 (2.1%)*
Other	*1 (0.8)*	*0*	*2 (1.6%)*	*3 (0.8%)*
Blinding of outcomes	*For the double-blind treatment, patients were supplied medication in the form of encapsulated tablets which appeared identical, and packed in identical bottles of 10 capsules. Where the dose was escalated, two bottles of medication were dispensed.* *The treatment code for each patient was concealed in a panel of each bottle label which was attached to the patient CRF at dispensing, and which could be opened in case of emergency. The randomisation code was not broken for any patient prior to database lock.*			

APRS: All Patients Randomised Set – all patients randomised in the study.

APTS: All patients Treated set – all randomised patients who took at least one dose of double-blind study product.

ITT: Intention to Treat – all randomised patients who took at least one dose of double blind study product and who had at least one post-baseline assessment of the MADRS total score.

** Percentages are relative to number of patients (N) in APTS population.*

2.5 Characteristics of comparative trials

The characteristics of the three listed trials are shown in Table 2.5.1.

Table 2.5.1 Characteristics of RCTs

Study No	Trial Design	Origin -Country	Disease Severity – Diagnosis and main inclusion criteria.	Treatment Regimens	Duration of study
99003	*Multi-national, double-blind, randomised, parallel-group. 1-week single-blind PBO run-in period prior to randomisation Flexible dose.*	*69 centres in 8 countries -3 in Canada, 22 in France, 17 in UK 3 in Belgium, 10 in Finland, 4 in Switzerland, 2 in Sweden and 8 in Norway.*	*Primary Care setting. Outpatients who fulfilled DSM-IV criteria: 296.2x and 296.3x where x=1, 2 or 3 for a MDD. A MADRS score≥22 and ≤40. Aged 18-65 inclusive.*	*Flexible dose. 10-20 mg ESC vs 20-40 mg CIT vs PBO Initial dose was 10mg of ESC or 20 mg CIT or PBO. At Week 4 or 6, investigators could increase dosage based on clinical response. After an increase, dose could be decreased due to AE's.*	*8 weeks following 1 week single blind PBO lead in period First patient visit: 15 September 1999 Last patient visit: 28 July 2000*
99022	*Multi-national, double-blind, randomised, parallel-group. 1-week single-blind PBO run-in period prior to randomisation Fixed dose.*	*66 active centres in 7 countries: 5 in Austria, 4 in Belgium, 6 in Denmark, 10 in France, 27 in Germany, 8 in Norway, and 6 in Sweden*	*Primary Care setting. Outpatients who fulfilled the DSM-IV criteria (296.2x or 296.3x, where x = 2 or 3) for MDD; had a MADRS score≥22; and Aged 18-65 years of age inclusive (19-65 years in Austria)*	*Fixed dose: 10 mg ESC vs 20 mg CIT vs*	*A one-week, single-blind, placebo run-in period, followed by: 24-week double blind treatment period followed by a 30 day safety assessment. First patient visit: 31 January 2000 Last patient visit: 21 May 2001*
MD01	*Double-blind randomised, parallel-group. 1-week single-blind PBO run-in period prior to randomisation. Fixed dose.*	*35 centres in US.*	*Secondary Care setting. Outpatients who fulfilled DSM-IV criteria. Aged 18-65 inclusive.*	*Fixed dose: 10 mg ESC vs 20 mg CIT vs 40 mg CIT vs PBO*	*8 weeks following 1 week single blind PBO lead in period First patient visit: 3 September 1999 Last patient visit: 2 June 2000*
MD02	*Double-blind randomised, parallel-group. 1-week single-blind PBO run-in period prior to randomisation Flexible dose.*	*22 centres in US.*	*Secondary Care setting. Outpatients who fulfilled DSM-IV criteria. Aged 18-80 inclusive.*	*Flexible dose 10-20 mg ESC vs 20-40 mg CIT vs PBO*	*8 weeks following 1 week single blind PBO lead in period First patient visit: 30 August 1999 Last patient visit: 23 May 2000*

MDD: Major Depressive Disorder, MADRS: Montgomery and Åsberg Depression Rating scale, AE: adverse event, UK: United Kingdom, US: United States of America, PBO: placebo.

Source: Lundbeck A/S Escitalopram – Clinical Expert Report – Report No 227/311,2000 – Final – 23 January 2001. Appendix IV, page 29-43

DSM-IV criteria: 296.2x and 296.3x where x=1, 2 or 3 for a MDD. 296.2=single MDD, 296.2=recurrent MDD. 1 = mild severity; 2=moderate severity; 3 severe without psychotic features [13]

Table 2.5.2 compares the characteristics of the trial population with the Australian population based on available ABS statistics:

The patient populations compare well with the Australian population who are currently on antidepressants.

The BEACH study[14] collects data from 999 general practitioners on 99,900 GP-patient encounters. These are used to describe aspects of general practice in Australia: the characteristics of the general practitioners and their patients; the types of services the GPs provide; the problems managed and the treatments provided at encounters.

In the BEACH report,[14] the patients presenting to a GP for depression were on average aged 48 years and 67% were female. These data agree well with data from the Australian Medical Index, which collects information on GP consultations.

The AMI data presents the demographics for patients who have been prescribed antidepressants in the 12 month period from September 2000-2001 by age and sex. By calculating the number and the midpoint of each age-group, the average age for males and females is 50, of which 67% were female.

The natural history of depression has been described in the National Health Priority Areas Report: Mental Health 1998.[15]

While there is little hard data on the disease course in Australia, the duration of the first episode of major depressive disorder has been reported in a US study. This was 181 weeks (42 months) on average for males and 114 weeks (26 months) for females.[15] While most people recover from their first episode with a median recovery time of three years, the majority will have at least one more episode of major depressive disorder in the following five years, with recurrence being the highest in earlier years.[15]

The findings in this study are consistent with the population in the studies being representative of the general population of depressed patients. It is apparent that MDD is a recurring condition and that episode duration tends to be between two to four years.

There is no information on the MADRS, HAMD or CGI-S that has been reported in the Australian setting. However we spoke with three psychiatrists Dr Rowan Davidson (WA), Professor Bob Goldney (SA) and Professor Gordon Parker who all agreed that the entry criteria for the trials of a MADRS of > 22 was acceptable for severe depression.

Thus, the results of the studies are likely to be generalisable to the Australian population who are on antidepressants for depression. The gender and age characteristics are very similar to the Australian population. While information on the disease course is unknown in Australia, it is highly likely that the study population is representative of patients with MDD in general.

Table 2.5.2 Comparison of demography of study populations and the Australians with MDD

	99003 (%)	99022 (%)	MD01 (%)	MD02 (%)	Australians on antidepressants (%)
%Female	72	74	65	53	68 (BEACH[c]) 67 (AMI[d])
Mean age	43	46	40	42	48 (BEACH[c]) 50 (AMI[d])
%Caucasian	99	99.2	84	83	Unknown
Weight (kg)	73	73	80	83	Unknown
MADRS score at baseline.	29	30 [e]	28.9	28.6	Unknown – see text
Mean CGI-S score at baseline.	4.3	4.25[f]	4.3	4.3	Unknown
Mean HAMD score at baseline.	Not performed	Not performed	25.5	24.9	Unknown
Mean duration MDD (years)	N/A	N/A	10.9 [a]	11.7[b]	Unknown – see text
Recurrent depressive episode %	N/A	Approx 50 [g]	70[a]	61[b]	Unknown – see text
Mean duration of episode (months)	N/A	N/A	20.0[a]	38.6[b]	Unknown – see text
Previous AD treatment %	N/A	N/A	51[a]	56[b]	Unknown

MADRS: Montgomery and Åsberg Depression Rating Scale
CGI-S; Clinical Global Impression - Severity
CGI-I; Clinical Global Impression – Improvement
N/A: Not available
[a]*Percentage of Safety population. Table 2.5, MD01 Study report, p 95*
[b]*Percentage of Safety population. Table 2.5, MD02 Study report, p 756*
[c] *Britt et al. 2001 p87-94* [14]
[d]*Source: Australian Medical Index supplied by IMS. July-September 2001*
[e] *Based on average of mean MADRS scores of 30.19 in CIT group and 29.48 in ESC arm at Day 0*
[f] *Based on average of mean CGI-S scores of 4.33 in CIT group and 4.16 in ESC arm at Day 0 (statistically significant difference)*
[g] *Based on page 50 of Study report*

2.6 Analysis of comparative randomised trials

Study Outcomes Evaluated

The results for the primary and secondary endpoints measured in the four RCTs comparing ESC and CIT are shown in Section Table 2.6.1. In three trials a PBO was included as one arm of the trial. These analyses were conducted comparing the treatments ESC or CIT with the PBO. In trial 99022, there was no PBO arm and escitalopram was compared directly with citalopram.

Efficacy endpoints

Study 99003

Primary endpoint

- *Change from baseline to final assessment of the MADRS total score*

Secondary endpoints

- *MADRS total score per visit*
- *Proportion of patients with at least a 50% reduction of the MADRS total score from baseline per visit (responders)*
- *Proportion of patients with a MADRS total score ≤12 per visit (complete remission)*
- *Clinical Global Impression Severity (CGI-S) score per visit*
- *Change from baseline to visit of CGI-S score*
- *Proportion of patients with a CGI-S score ≤2 per visit*
- *Clinical Global Impression Improvement (CGI-I) score per visit*
- *Proportion of patients with a CGI-I score ≤2 per visit*
- *Change from baseline to final assessment of all MADRS single items*

Study 99022

Primary endpoint

- *the development of the MADRS total scores during the 24 weeks of double-blind treatment (using repeated measures analysis on the observed cases (OC) data)*

Secondary endpoints

- *Change in MADRS total score from baseline to each assessment and to final assessment;*

- *Proportion of patients with at least a 50% reduction in MADRS total score from baseline per visit and at final assessment (responders);*
- *Proportion of patients with a MADRS total score ≤12 per visit and at final assessment (remitters);*
- *Change from baseline to final assessment in MADRS single items;*
- *Clinical Global Impressions – Severity (CGI-S) scores (at final assessment; and change from baseline to each visit and to final assessment);*
- *Hamilton Anxiety Scale (HAMA) scores (at final assessment; and change from baseline to each visit and to final assessment)*

Studies MD01 and MD02

Primary endpoint

- *Change from baseline to week 8 of the MADRS total score*

Secondary endpoints

- *Change from baseline to week 8 in Hamilton Depression Rating Scale (HAMD)*
- *Change from baseline to week 8 in HAMD depressed mood item*
- *Change from baseline to week 8 in Clinical Global Impressions (CGI) Scale – for Improvement (CGI-I)*
- *Change from baseline to week 8 in Clinical Global Impressions (CGI) Scale – for Severity (CGI-S)*

Rating scales used to assess efficacy

Montgomery Asberg Depression Rating Scale (MADRS)[17]

The MADRS total score was used as the primary efficacy endpoint in all three trials.

The MADRS consists of 10 items assessing feelings of sadness, lassitude, pessimism, inner tension, suicidality, reduced sleep or appetite, difficulty in concentration, and lack of interest. All are core symptoms of depression and measure the severity of the depressive episode for the previous 7 days. The instrument is administered by a trained rater.

Each item is scored on a 7-point scale with a score of 0 reflecting no symptoms and a score of 6 reflecting symptoms of maximum severity. The minimum total score was 22 for inclusion into the study. Nine of the items are based on patient report and one is based on the rater's observation.

A copy of the questionnaire is attached in Appendix 3.

Clinical Global Impressions (CGI)[18]

The CGI is one of the most commonly used brief assessment tools in psychiatry.

The CGI Severity scale (CGI-S) rates the severity of the patient's current state of mental illness based on the investigator's clinical opinion with regard to a patient population with Major Depressive Disorder.

The CGI-S scale is from 1 (normal) to 7 (most severely ill).

The CGI-I measures subsequent changes as assessed by the same rater throughout the trial. On a 7 point rating scale, 1=very much improved; 2=improved; 3 =minimally improved; 4=not changed, 5=minimally worsened, 6=worsened; 7=very much worse.

Hamilton Depression Rating Scale (HAMD) 24-item

The HAMD[19] is the most widely used rating scale for the assessment of depression symptoms. The scale was used as a secondary endpoint in Studies MD01 and MD02. This 24-item scale rates the patient's depressive state based on feelings of depression, guilt, suicidality, anxiety, agitation, helplessness, hopelessness, worthlessness, or depersonalization/derealization, their level of insight, their patterns of insomnia, loss of interest in work and other activities, weight loss, hypochondriasis, psychomotor retardation, or the presence of paranoid, obsessive-compulsive, genital, or somatic symptoms, and diurnal variation in the presence of symptoms.

Each item was scored on a 3, 4, or 5-point scale with 0 reflecting no symptoms and higher scores reflecting increasing symptom severity. A minimum score of 2 out of 4 on the depressed mood item (item 1) was also necessary for study inclusion.

In addition, the depressed mood item (item 1) was used as an outcome measure.

Hamilton Anxiety Scale (HAMA)

The HAMA rating scale consists of 14 items, each rated on a scale from 0 to 4. Each item is illustrated by several non-limitative examples and has to be globally rated taking into account its severity, nature, and frequency. The rating should be based on actual symptomatic features such as signs observed during the interview and symptoms reported by the patient. The time period explored with this scale is the previous 7 days.

Statistical analysis

Study 99003

The data set comprised of three analysis sets:

All Patients Randomised Set (APRS),

All Patients Treated Set (APTS); and the

- *Full Analysis Set (FAS) which included all randomised patients who took at least one dose of double blind study product and who had at least one post-baseline assessment of the MADRS total score.*

The FAS is the same as the Intention to Treat (ITT) population and will be referred to as such for the remainder of the document.

All efficacy analyses were conducted on the ITT set. The primary efficacy endpoint, the change in MADRS total score from baseline, was analysed using a general linear model, using all three treatment groups, for analysis of covariance with factors for treatment group (TREAT), collective centres (CCENTRE), and treatment by collective centres interaction (TREAT*CCENTRE), and with baseline based on a score as a covariate. All centres that did not contribute to all three treatment groups and did not contribute with at least 4 patients in the full-analysis set were merged into a single collective centre.

The secondary endpoints, the CGI-S and CGI-C were analysed in the same way as the change in MADRS total score from baseline. In addition the CGI-S and CGI-I were analysed using the non-parametric Cochran-Mantle-Haenszel statistic with modified ridit scores with individual CCENTRES comprising the strata.

Missing data were replaced using the Last Observed Carried Forward (LOCF) where missing values for post-baseline MADRS, CGI-I, and CGI-S assessments were imputed by the value observed immediately prior to the missing value.

If the number of missing MADRS 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 MADRS score was regarded as missing.

All safety analyses were conducted for the APTS.

Adjustments for Multiple Comparisons

No adjustment was made for multiple endpoints as the primary efficacy analysis was only between escitalopram and placebo. Only the p-value from the primary analysis was confirmatory and all other analyses were supportive or exploratory.

Studies MD01 and MD02

Efficacy analyses were performed on the ITT data set, which included all patients in safety population who had at least one post-baseline efficacy assessment on the MADRS. All tests were 2-sided with a 5% significance level for main effects and 10% significance level for interaction terms.

All week 8 analyses were conducted using the LOCF approach. In addition to LOCF, an observed cases (OC) approach was used, in which only observed values were analysed. Missing values were imputed using the LOCF approach. Missing assessments at post baseline visits were imputed using the last observed non-missing value prior to the missing value. If the missing value occurred at week 1 and there was at least one subsequent post-baseline assessment available, the baseline value was carried forward for week 1. For each efficacy parameter, only the total score, not individual items, was carried forward.

The primary efficacy parameter was the change from baseline to week 8 in the MADRS total score. Comparisons of escitalopram 10 mg/day, escitalopram 20 mg/day, and placebo were performed using an analysis of covariance (ANCOVA)

model with treatment (escitalopram 10 mg/day, escitalopram 20 mg/day, and placebo), study centre, and the treatment by centre interaction as factors and the baseline score as covariate. The interaction term was dropped from the model if it was not significant at the 10% level. Pairwise comparisons (escitalopram 10 mg/day vs. placebo, escitalopram 20 mg/day vs. placebo) were considered significant only if the overall p-value was significant. The p-values from SAS Type III analysis are presented, along with the difference in least squares means (LSM) between the two treatment groups and 95% confidence intervals (CI).

The secondary parameters, HAMD, CGI-S, and HAMD depressed mood item at week 8 were analysed using an ANCOVA model, as described for the primary efficacy parameter. A two-way analysis of variance (ANOVA) model was used for the CGI-I score at Week 8, since this parameter records improvement relative to baseline and is not applicable at baseline.

Study sites with ≤ 2 patients in any treatment group in the ITT population were pooled into a single centre.

In study MD02, no centres were pooled for the primary efficacy analysis. Upon review of the individual site results, a high degree of variability in the placebo response was observed among centres with small patient samples. In order to minimise the impact of small sites with high variability a post-hoc analysis was conducted in which sites with 3 or fewer patients in the ITT population in any treatment group were pooled into a single centre.

Safety analyses were performed on the safety population.

Study 99022

The data set comprised of four analysis sets:

- *All Patients Randomised Set (APRS),*
- *All Patients Treated Set (APTS);*
- *Full Analysis Set (FAS) which included all randomised patients who took at least one dose of double blind study product and who had at least one post-baseline assessment of the MADRS total score; and the*
- *Per-protocol set (PPS) – all randomised patients who had no major protocol violations.*

The FAS is the same as the Intention to Treat (ITT) population and will be referred to as such for the remainder of the document. As the difference between the size of the FAS and the PPS did not exceed 20%, it was not found necessary to perform efficacy analyses on the PPS.

All efficacy analyses were conducted on the ITT set. To adjust for any baseline imbalance between treatment groups, efficacy analyses were carried out including baseline values as covariates.

Primary efficacy analysis

Variance analyses of the MADRS total scores were performed. The hypothesis of interest was the hypothesis of non-inferiority of escitalopram to citalopram. Repeated

measures analysis was used to model and compare the treatment groups over all assessment points simultaneously. Mean structure testing was performed by maximum likelihood estimation and covariance structure testing was performed by restricted maximum likelihood estimation.

The initial model included an overall intercept term (INTERCEPT) to describe the baseline level with CCENTRE and TIME as explanatory variables. The treatment effect was modelled as increasing linearly to Week 8 and stabilizing thereafter.

$$E\{MA\_SCORE\} = INTERCEPT + CCENTRE + TIME + CCENTRE*TIME + CCENTRE*TIME2 + TREAT*TIME2$$

The time covariates are defined below:

- TIME – weeks
- TIME2 – equal to TIME up to Week 8, and 8 thereafter

Initially, an unstructured covariance matrix was used to describe the correlation between assessments within patients. It was investigated whether this covariance structure could be simplified to a mixed effects model with random intercept and random slopes for each patient with cut points at Week 4 and Week 8. If this proved possible, it was to be investigated whether this could be further simplified to only a random effect of PATIENT (that is, a random intercept).

With respect to the mean structure, the hypothesis of interest was the hypothesis of non-inferiority of escitalopram to citalopram as measured by the difference of the estimates for TREAT*TIME2. As stated in the protocol, the clinically relevant difference between escitalopram and citalopram is 3 points on the MADRS scale at the final visit. With a linearly increasing treatment difference up to Week 8 and an equal difference at all later time points, this corresponds to a difference between the slope parameters for TREAT*TIME2 of 0.375 (= 3/8). So it would be concluded that escitalopram was not inferior to citalopram if the difference between the slope parameters for escitalopram and citalopram (slope for escitalopram minus slope for citalopram) could be shown by a one-sided 95% confidence interval to be smaller than 0.375.

Substantially higher numbers of withdrawals in one group than in the other were controlled for by also looking at the difference in withdrawal profiles between the two treatment groups (i.e. number of withdrawals and time of withdrawal) as well as performing a traditional last observation carried forward (LOCF) analysis on the last assessment.

Secondary efficacy analysis

The change from baseline in MADRS total score was analysed by analysis of covariance (ANCOVA) based on a general linear model, with factors for treatment group, ccentre,and treatment-by-ccentre interaction as well as age, baseline BMI, baseline weight, sex, and baseline MADRS total score. 2 tests were performed on the proportion of patients who were remitters and responders. As with the MADRS total score, the change in CGI-S was analysed by ANCOVA; in addition a Cochran-

Mantel-Haenszel test was performed for CGI-S at the final assessment. For the HAMA total score, ANCOVA of change was performed.

In addition to $\chi 2$ tests, the number of remitters and responders were also analysed using a logistic regression model adjusting for ccentre and baseline MADRS score. This was done for the final measurement as well as for LOCF at Week 8.

ANCOVA of the MADRS total score was performed in subgroups of patients (severely and moderately ill).

Handling of Missing Data and Withdrawals

In general, for analyses using LOCF, missing values for post-baseline MADRS assessments were imputed by the value observed immediately prior to the missing value. If the number of missing MADRS 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 MADRS score was regarded as missing.

Adjustments for Multiple Comparisons

No adjustment was made for multiple endpoints as the primary efficacy analysis was only between escitalopram and citalopram. Only the p-value from the primary analysis was confirmatory and all other analyses were supportive or exploratory.

Safety analysis

Safety was evaluated on the basis of adverse events, clinical laboratory tests, ECG parameters, and vital signs in the escitalopram and citalopram groups. All safety analyses were conducted for the APTS.

Table 2.6.1 Efficacy outcomes of Study 99003

Study No	Study endpoints	Results (ITT-LOCF)	Source
99003	Flexible dose. 10-20 mg ESC vs. 20-40 mg CIT vs. PBO Initial dose was 10mg of ESC or 20 mg CIT or PBO. At Week 4 or 6, investigators could increase dosage based on clinical response. After an increase, dose could be decreased due to AE's.		
	Primary		
99003	**MADRS** – Least squares mean change from baseline to final assessment (95%CI).	PBO -12.11 (-13.44 -10.78) CIT -13.59 (-14.91 -12.27) ESC -15.02 (-16.35 -13.69)	Integrated Clinical Study Report: for 99003: Panel 12
	MADRS – Difference in mean change from baseline to final assessment (95%CI).	CIT-PBO -1.48 (-3.30;0.33) p=0.109 ESC-PBO -2.91 (-4.73;-1.09) p= 0.002	Integrated Clinical Study Report: for 99003: Panel 13
	Secondary		
	Adjusted mean change from baseline in MADRS Total Score per visit	See Figure 2.6.1	
	Difference of the Adjusted Mean Changes from Baseline in MADRS Total Score per visit	See Figure 2.6.2	
	Proportion (%) of patients with at least 50% reduction of the MADRS total score from baseline (responders) (95%CI). LOCF	PBO 43.5 (35.5 -51.7) CIT 49.7 (41.7 -57.7) ESC 61.3 (53.1-69.0)	Integrated Clinical Study Report: Panel 18
	Difference in proportion (%) of patients with at least 50% reduction of the MADRS total score from baseline (responders) (95%CI). LOCF	CIT-PBO 6.2 (-4.9;17.2) p=0.308 ESC-PBO 17.8 (6.8;28.7) p= 0.002	Integrated Clinical Study Report: for 99003: Panel 19

	Proportion (%) of patients with a MADRS score ≤12 (complete remission) (95%CI). LOCF	*PBO 40.9 (33.1;49.1)* *CIT 39.6 (32.0;47.7)* *ESC 50.3 (42.2;58.4)*	*Integrated Clinical Study Report: for 99003: Table 27*
	Difference in proportion (%) of patients with at MADRS score ≤12 (complete remission) (95%CI). LOCF	*CIT-PBO -1.3 (-12.2;9.6) p=0.819* *ESC-PBO 9.4 (-1.6;20.5) p=0.110*	*Integrated Clinical Study Report: for 99003: Table 29*
	***CGI-S** Adjusted change from baseline to visit of CGI-S score*	*PBO -1.41 (-1.59;-1.22)* *CIT -1.56 (-1.74;-1.37)* *ESC -1.79 (-1.98;-1.61)*	*Integrated Clinical Study Report: for 99003: Panel 21*
	***CGI-S** Difference in adjusted change from baseline in CGI-S scores (95%CI). LOCF*	*CIT-PBO -0.15 (-0.40;0.10) p=0.245* *ESC-PBO -0.38 (-0.64;-0.13) p=0.003*	*Integrated Clinical Study Report: for 99003: Panel 22*
	***CGI-I** Adjusted change from baseline to visit of CGI-I score*	*PBO 2.51 (2.33;2.68)* *CIT 2.20 (2.02;2.38)* *ESC 2.08 (1.90;2.26)*	*Integrated Clinical Study Report: for 99003: Panel 24*
	***CGI-I** Difference in adjusted change from baseline in CGI-I scores (95%CI). LOCF*	*CIT-PBO -0.31 (-0.55;-0.06) p=0.014* *ESC-PBO -0.43 (-0.67;-0.18) p=0.001*	*Integrated Clinical Study Report: for 99003: Panel 25*
	***CGI-I** Proportion (%) of patients with a CGI-I score ≤2 (95%CI). LOCF*	*PBO 54.5 (46.3;62.6)* *CIT 64.8 (56.8;72.2)* *ESC 72.9 (65.2;79.7)*	*Integrated Clinical Study Report: for 99003: Table 44*
	***CGI-I** Difference in proportion (%) of patients with CGI-I score ≤2 (95%CI). LOCF*	*CIT-PBO 10.2 (-0.6;21.0) p=0.067* *ESC-PBO 18.4 (7.8;28.9) p=0.001*	*Integrated Clinical Study Report: for 99003: Table 45*

ESC: Escitalopram, CIT: Citalopram, ITT: Intention to treat, HAMD: Hamilton Depression Rating Scale, CGI: Clinical Global Impressions, AE: Adverse Event, ECG: electocardiogram, PBO: Placebo, OC: Observed cases, LOCF: Last observation carried forward, ANCOVA: analysis of covariance, ANOVA: Analysis of variance, CMH:Cochran-Mantle-Haenszel, APRS: All Patients Randomised Set – all patients randomised in the study., APTS: All patients Treated set – all randomised patients who took at least one dose of double-blind study product., FAS – all randomised patients who took at least one dose of double blind study product and who had at least one post-baseline assessment of the MADRS total score.

Table 2.6.2 Efficacy outcomes of Study MD01

		ITT-LOCF	Source
MD01 (99007)	Fixed dose: 10 mg ESC vs 20 mg ESC vs 40 mg CIT vs PBO		
	Primary		
	MADRS – Change from baseline to Week 8 (95%CI).	PBO -9.4 (-11.1; -7.7) CIT -12.0 (-13.8;-10.2) ESC 10mg -12.8 (-14.3;-11.3) ESC 20mg -13.9 (-15.5; -12.3)	MD01 Reports and Tables 030762, p66. Table 3.1 Nb: CI calculated as 1.96 x SEM
	MADRS – Difference in mean change from baseline to Week 8 (95%CI).	CIT-PBO -2.5 (-5.0;-0.1) p=0.0414 ESC 10mg-PBO -3.9 (-6.2;-1.7) p= 0.0007 ESC 20mg-PBO -4.6 (-6.9;-2.4) p= <0.0001	MD01 Reports and Tables 030762, p99. Table 3.1
	Secondary		
	HAMD– Change from baseline to Week 8 (95%CI).	PBO -7.6 (-9.1; -6.1) CIT -9.9 (-11.6;-8.2) ESC 10mg -10.2 (-11.6;-8.8) ESC 20mg -11.7 (-13.2; -10.2)	MD01 Reports and Tables 030762, p120. Nb: CI calculated as 1.96 x SEM
	HAMD– Difference in mean change from baseline to Week 8 (95%CI).	CIT-PBO -2.2 (-4.3;-0.0) p=0.0518 ESC 10mg-PBO -3.3 (-5.2;-1.3) p= 0.0014 ESC 20mg-PBO -4.1 (-6.0;-2.1) p= <0.0001	MD01 Reports and Tables 030762, p120. Table 4.2A.
	HAMD Depressed mood item – Change from baseline to Week 8 LOCF (95%CI).	PBO -0.9 (-1.1; -0.7) CIT -1.4 (-1.6;-1.2) ESC 10mg -1.3 (-1.5; -1.1) ESC 20mg -1.4 (-1.6; -1.2)	MD01 Reports and Tables 030762, p132. Table 4.5A. Nb: CI calculated as 1.96 x SEM

	HAMD *– Depressed mood item - Difference in mean change from baseline to Week 8 LOCF (95%CI).*	*CIT-PBO -0.5 (-0.7; -0.2) p=0.0005* *ESC 10mg-PBO -0.5 (-0.7; -0.2) p=0.0006* *ESC 20mg-PBO -0.5 (-0.8; -0.3) p= <0.0001*	*MD01 Reports and Tables 030762, p132. Table 4.5A.*
	CGI-I *scale– Change from baseline to Week 8 LOCF (95%CI).*	*PBO 3.0 (2.8; 3.2)* *CIT 2.6 (2.4; 2.8)* *ESC 10mg 2.5 (2.3; 2.7)* *ESC 20mg 2.4 (2.2; 2.6)*	*MD01 Reports and Tables 030762, p124. Table 4.3A.*
	CGI-I *scale– Difference in mean change from baseline to Week 8 LOCF (95%CI).*	*CIT-PBO -0.4 (-0.7;-0.1) p=0.0140* *ESC 10mg-PBO -0.5 (-0.8;-0.2) p= 0.0007* *ESC 20mg-PBO -0.6 (-0.8;-0.3) p= <0.0001*	*MD01 Reports and Tables 030762, p124. Table 4.3A.*
	CGI-S *scale– Change from baseline to Week 8 LOCF (95%CI).*	*PBO -0.8 (-1.0; -0.6)* *CIT -1.2 (-1.4;-1.0)* *ESC 10mg -1.3 (-1.5;-1.1)* *ESC 20mg -1.4 (-1.6; -1.2)*	*MD01 Reports and Tables 030762, p128. Table 4.4A.*
	CGI-S *scale– Difference in mean change from baseline to Week 8 LOCF (95%CI).*	*CIT-PBO -0.3 (-0.6;-0.0) p=0.0266* *ESC 10mg-PBO -0.5 (-0.8;-0.3) p= 0.0002* *ESC 20mg-PBO -0.6 (-0.8;-0.3) p= <0.0001*	*MD01 Reports and Tables 030762, p128. Table 4.4A.*

ESC: Escitalopram, CIT: Citalopram, ITT: Intention to treat, HAMD: Hamilton Depression Rating Scale, CGI: Clinical Global Impressions, AE: Adverse Event, ECG: electocardiogram, PBO: Placebo, OC: Observed cases, LOCF: Last observation carried forward, ANCOVA: analysis of covariance, ANOVA: Analysis of variance, CMH:Cochran-Mantle-Haenszel, APRS: All Patients Randomised Set – all patients randomised in the study., APTS: All patients Treated set – all randomised patients who took at least one dose of double-blind study product., FAS – all randomised patients who took at least one dose of double blind study product and who had at least one post-baseline assessment of the MADRS total score.

Table 2.6.3 Efficacy outcomes of Study MD02

		ITT-LOCF	ITT-OC	Source
MD02 (99008)	Flexible dose; 10-20 mg ESC vs 20-40 mg CIT vs PBO			
	Primary			
	MADRS – Change from baseline to Week 8 (95%CI).	PBO -11.2 (-13.0; -9.4) CIT -13.0 (-14.8;-11.2) ESC -12.9 (-14.7;-11.1)	PBO -11.8 (-13.7; -9.9) CIT -14.1 (-15.9;-12.3) ESC -15.1 (-16.9;-13.3)	MD02 Statistical Analysis Tables 030793, p777. Table4.1A Nb: CI calculated as 1.96 x SEM
	MADRS – Difference in mean change from baseline to Week 8 (95%CI).	CIT-PBO -1.9 (-4.4; 0.7) p=0.151 ESC-PBO -1.4 (-3.9; 1.0) p=0.251	CIT-PBO -2.7 (-5.3; 0.0) p=0.05 ESC-PBO -2.9 (-5.5; -0.2) p=0.032	MD02 Statistical Analysis Tables 030793, p777. Table4.1A P780 Table 4.1B (OC)
	Secondary			
	HAMD– Change from baseline to Week 8 (95%CI).	PBO -9.6 (-11.2; -8.0) CIT -11.4 (-12.9;-9.9) ESC -10.4 (-12.0;-8.8)	PBO -10.2 (-11.9; -8.5) CIT -12.4 (-14.0;-10.8) ESC –12.3 (-14.0;-10.6)	MD02 Statistical Analysis Tables 030793, p783. Table4.2A Nb: CI calculated as 1.96 x SEM
	HAMD– Difference in mean change from baseline to Week 8 (95%CI).	CIT-PBO -2.0 (-4.2;0.1) p=0.068 ESC-PBO -0.7 (-2.8; 1.4) p=0.506	CIT-PBO -2.6 (-4.8;-0.31) p=0.027 ESC-PBO -1.9 (-4.1; 0.4) p=0.100	MD02 Statistical Analysis Tables 030793, p783. Table 4.2A. P786 Table 4.2B (OC)
	HAMD Depressed mood item – Change from baseline to Week 8 LOCF (95%CI).	PBO -1.1 (-1.3; -0.9) CIT -1.3 (-1.5;-1.1) ESC -1.2 (-1.4; -1.0)	PBO -1.2 (-1.4; -1.0) CIT -1.5 (-1.7; -1.3) ESC -1.5 (-1.7; -1.3)	MD02 Statistical Analysis Tables 030793, p799. Table 4.5A. Nb: CI calculated as 1.96 x SEM

	HAMD – Depressed mood item *- Difference in mean change from baseline to Week 8 LOCF (95%CI).*	*CIT-PBO -0.4 (-0.7; -0.0) p=0.024* *ESC-PBO -0.1 (-0.4; 0.2) p=0.439*	*CIT-PBO -0.4 (-0.7; -0.1) p=0.013* *ESC-PBO -0.3 (-0.6; 0.0) p=0.039*	*MD02 Statistical Analysis Tables 030793, p799. Table 4.5B.*
	CGI-I scale*– Change from baseline to Week 8 LOCF (95%CI).*	*PBO 2.6 (2.4; 2.8)* *CIT 2.3 (2.1; 2.5)* *ESC 2.5 (2.3; 2.7)*	*PBO 2.6 (2.4; 2.8)* *CIT 2.2 (2.0; 2.4)* *ESC 2.3 (2.1; 2.5)*	*MD02 Statistical Analysis Tables 030793, p788. Table 4.3A.*
	CGI-I scale*– Difference in mean change from baseline to Week 8 LOCF (95%CI).*	*CIT-PBO -0.4 (-0.6;-0.1)p=0.0160* *ESC-PBO -0.1 (-0.4;0.2) p= 0.466*	*CIT-PBO -0.4 (-0.7;-0.1)p=0.007* *ESC-PBO -0.3 (-0.6;0.0) p= 0.081*	*MD02 Statistical Analysis Tables 030793, p788. Table 4.3A.*
	CGI-S scale*– Change from baseline to Week 8 LOCF (95%CI).*	*CIT -1.5 (-1.7;-1.3)* *PBO -1.1 (-1.3; -0.9)* *ESC -1.3 (-1.5;-1.1)*	*CIT -1.7 (-2.0;-1.4)* *PBO -1.2 (-1.4; -1.0)* *ESC -1.5 (-1.7;-1.3)*	*MD02 Statistical Analysis Tables 030793, p793. Table 4.4A.*
	CGI-S scale*– Difference in mean change from baseline to Week 8 LOCF (95%CI).*	*CIT-PBO -0.4 (-0.7;-0.0) p=0.024* *ESC -PBO -0.1 (-0.4;0.2) p=0.439*	*CIT-PBO -0.5 (-0.8;-0.1) p=0.005* *ESC -PBO -0.3 (-0.6;0.0) p=0.061*	*MD02 Statistical Analysis Tables 030793, p793. Table 4.4A.*

ESC: Escitalopram, CIT: Citalopram, ITT: Intention to treat, HAMD: Hamilton Depression Rating Scale, CGI: Clinical Global Impressions, AE: Adverse Event, ECG: electocardiogram, PBO: Placebo, OC: Observed cases, LOCF: Last observation carried forward, ANCOVA: analysis of covariance, ANOVA: Analysis of variance, CMH:Cochran-Mantle-Haenszel, APRS: All Patients Randomised Set – all patients randomised in the study., APTS: All patients Treated set – all randomised patients who took at least one dose of double-blind study product., FAS – all randomised patients who took at least one dose of double blind study product and who had at least one post-baseline assessment of the MADRS total score.

Table 2.6.4 Efficacy outcomes of Study 99022

Study endpoints	Results (ITT-OC)	Source
Fixed dose. 10mg ESC vs. 20 mg CIT. Duration 24 weeks.		
Primary		
***MADRS** - Change from baseline to final assessment of the total score*	*Figure 2.6.3. The upper confidence limit for the slope parameter for escitalopram minus the slope parameter for citalopram was 0.119, which is smaller than the 0.375 required for non-inferiority. Escitalopram was thus at least as efficacious as citalopram.*	*Integrated Clinical Study Report: for 99022: Panel 15*
Secondary		
***MADRS** - Change from baseline to each assessment in total score.*	*Figure 2.6.4. There were no statistically significant differences between treatment groups in the adjusted mean change from baseline at any time point.*	*Integrated Clinical Study Report: for 99022: Panel 19, p58*
***MADRS** - Change from baseline to final assessment in total score (Day 168)*	*CIT -23.44* *ESC -23.32 Difference to CIT =0.12 (95%CI: -10.2-1.25) p=0.838* *Results from the ANCOVA of the change in the MADRS total score from baseline to final assessment was based on a general linear model with factors for treatment group, centre, and treatment-by-centre interaction, as well as age, baseline BMI, baseline weight, sex, and baseline MADRS total score. Testing for interaction between centre and treatment (CCENTRE*TREAT) at final assessment did not reveal any significant interaction (p = 0.52).*	*Integrated Clinical Study Report: for 99022: Panel 19, p58*
***MADRS** - Proportion of patients with at least a 50% reduction of the total score (responders) from baseline per visit.*	*See Figure 2.6.5. There was no statistically significant difference between treatment groups in the proportion of responders at any time point (OC or LOCF).*	*Integrated Clinical Study Report: for 99022: Panel 21. p61*
***MADRS** - Proportion of patients with at least a 50% reduction of the total score from baseline to final assessment (responders) (Day 168)*	*CIT 91.1* *ESC 87.6 Difference to CIT =3.5 (95%CI: -3.7-10.7) p=0.440*	*Integrated Clinical Study Report: for 99022: Panel 21. p61*

MADRS *- Proportion of patients with a total score ≤ 12 (remitters) per visit*	*See Figure 2.6.6. There was no statistical difference between treatment groups in the proportion of remitters at any time point (OC or LOCF).*	*Integrated Clinical Study Report: for 99022: p62 and Table 24. p170*
MADRS *- Proportion of patients with a total score ≤ 12 (remitters) at final assessment (Day 168).*	*CIT 82.2* *ESC 83.4 Difference to CIT =-1.2 (95%CI: -10.1-7.6) p=0.874*	*Integrated Clinical Study Report: for 99022: Table 24. p170*
MADRS *- Change from baseline to final assessment of all single items*	*See Figure 2.6.7. For escitalopram, borderline statistical superiority was found for item 10 (suicidal thoughts, p = 0.053). In all, eight of the 10 items were numerically superior for escitalopram (items 1, 2, 4, 5, 6, 7, 8, and 10).*	*Integrated Clinical Study Report: for 99022. Panel 26. p67*
CGI-S - *score per visit*	*See Figure 2.6.8.*	*Integrated Clinical Study Report: for 99022: Table 31. p181*
CGI-S *- Change from baseline to visit of score*	*See Figure 2.6.9.*	*Integrated Clinical Study Report: for 99022: Table 35, p191*
CGI-S *- Change from baseline to final assessment in score*	*CIT –2.57* *ESC –2.67 Difference to CIT =-0.10 (95%CI: -0.26- 0.07) p=0.874*	*Integrated Clinical Study Report: for 99022: Table 35, p191*
HAMA *scores per visit*	*See Figure 2.6.10.*	*Integrated Clinical Study Report: for 99022: Table 43, p204*
HAMA - *scores at final assessment*	*CIT –19.70* *ESC –19.42 Difference to CIT =-0.29 (95%CI: -0.93- 1.50) p=0.643*	*Integrated Clinical Study Report: for 99022: Table 43, p204*

ESC: Escitalopram, CIT: Citalopram, ITT: Intention to treat, HAMD: Hamilton Depression Rating Scale, CGI: Clinical Global Impressions, AE: Adverse Event, ECG: electocardiogram, PBO: Placebo, OC: Observed cases, LOCF: Last observation carried forward, ANCOVA: analysis of covariance, ANOVA: Analysis of variance, CMH:Cochran-Mantle-Haenszel, APRS: All Patients Randomised Set – all patients randomised in the study., APTS: All patients Treated set – all randomised patients who took at least one dose of double-blind study product., FAS – all randomised patients who took at least one dose of double blind study product and who had at least one post-baseline assessment of the MADRS total score., HAMA - Hamilton Anxiety Scale., CGI-S - Clinical Global Impression Severity

Table 2.6.5. Study 99003 - Adjusted Mean Change from Baseline in MADRS Total Scores

Treatment Difference	Visit @		Least Squares Mean	SE	95% Confidence Limits Lower	Upper	p-value
CIT-PBO	Week 1	(OC)	-0.79	0.56	-1.89	0.31	0.160
	Week 2	(OC)	-0.71	0.69	-2.06	0.64	0.304
	Week 3	(OC)	-0.90	0.81	-2.49	0.68	0.264
	Week 4	(OC)	-1.44	0.86	-3.13	0.25	0.095
	Week 6	(OC)	-1.40	0.86	-3.10	0.30	0.105
	Week 8	(OC)	-1.01	0.88	-2.75	0.73	0.252
	Last	(LOCF)	-1.48	0.92	-3.30	0.33	0.109
ESC-PBO	Week 1	(OC)	-1.27	0.56	-2.37	-0.17	0.023
	Week 2	(OC)	-1.44	0.69	-2.80	-0.09	0.037
	Week 3	(OC)	-1.79	0.82	-3.39	-0.18	0.029
	Week 4	(OC)	-2.77	0.87	-4.48	-1.06	0.002
	Week 6	(OC)	-2.56	0.87	-4.27	-0.85	0.003
	Week 8	(OC)	-2.35	0.89	-4.11	-0.59	0.009
	Last	(LOCF)	-2.91	0.93	-4.73	-1.09	0.002

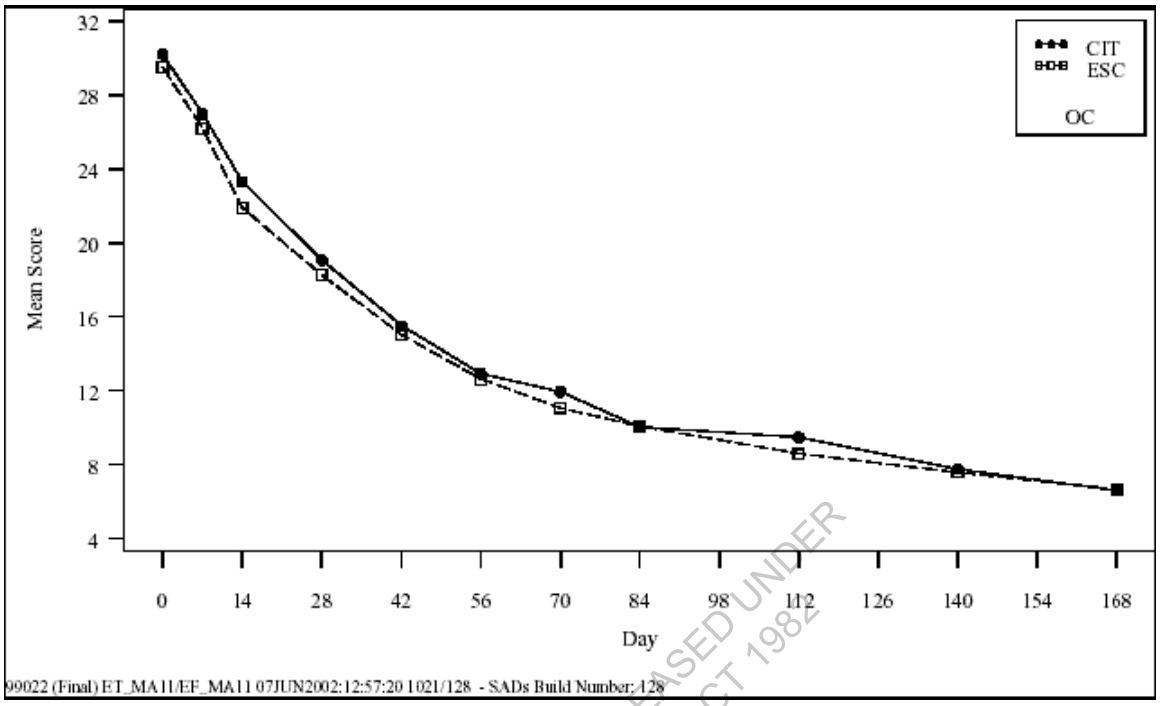
@ visit windows
The primary efficacy analysis is defined by testing
the adjusted treatment difference ESC-PBO at last visit
Model: ANCOVA with treatment and ccentre as factors
and baseline score as covariate
Note: ccentre is identical to centre except for small centres, which are pooled

Table 2.6.6. Study 99003 - Treatment Difference of the Adjusted Mean Changes from Baseline in MADRS Total Score

Treatment Group	Visit @		n	Least Squares Mean	SE	95% Confidence Limits Lower	Upper
PBO	Week 1	(OC)	149	-3.13	0.41	-3.94	-2.33
	Week 2	(OC)	140	-6.76	0.51	-7.76	-5.75
	Week 3	(OC)	141	-8.84	0.59	-10.01	-7.66
	Week 4	(OC)	144	-9.06	0.63	-10.31	-7.81
	Week 6	(OC)	145	-11.18	0.63	-12.43	-9.94
	Week 8	(OC)	138	-13.54	0.66	-14.84	-12.24
	Last	(LOCF)	154	-12.11	0.67	-13.44	-10.78
CIT	Week 1	(OC)	154	-3.92	0.40	-4.72	-3.12
	Week 2	(OC)	150	-7.46	0.49	-8.44	-6.49
	Week 3	(OC)	151	-9.74	0.58	-10.89	-8.59
	Week 4	(OC)	154	-10.50	0.62	-11.72	-9.27
	Week 6	(OC)	148	-12.59	0.63	-13.84	-11.33
	Week 8	(OC)	150	-14.55	0.64	-15.81	-13.29
	Last	(LOCF)	159	-13.59	0.67	-14.91	-12.27
ESC	Week 1	(OC)	154	-4.40	0.40	-5.20	-3.61
	Week 2	(OC)	146	-8.20	0.50	-9.18	-7.22
	Week 3	(OC)	143	-10.62	0.60	-11.80	-9.45
	Week 4	(OC)	145	-11.82	0.63	-13.07	-10.58
	Week 6	(OC)	144	-13.74	0.63	-15.00	-12.49
	Week 8	(OC)	145	-15.89	0.64	-17.15	-14.62
	Last	(LOCF)	155	-15.02	0.67	-16.35	-13.69

@ visit windows
Model: ANCOVA with treatment and ccentre as factors
and baseline score as covariate
Test for treatment by ccentre interaction at last visit (LOCF): p=0.6155
Note: ccentre is identical to centre except for small centres, which are pooled

Figure 2.6.1. Study 99022 - MADRS Total Score (FAS, OC)



Source Integrated Clinical Study Report Panel 15, p54

Table 2.6.7. Study 99022 - Treatment Difference in Adjusted Mean Change from Baseline of MADRS Total Score (FAS, OC)

Treatment Group	Day @	n	Least Squares Mean	Difference to CIT	SE	95% Confidence Limits Lower	Upper	p-value
CIT	7	172	-3.17					
	14	165	-6.95					
	28	164	-11.27					
	42	156	-14.58					
	56	153	-17.36					
	70	146	-18.28					
	84	142	-20.19					
	112	143	-20.79					
	140	138	-22.35					
	168	135	-23.44					
ESC	7	163	-3.42	-0.25	0.45	-1.15	0.64	0.575
	14	157	-7.94	-0.99	0.56	-2.09	0.11	0.078
	28	154	-11.77	-0.51	0.65	-1.79	0.78	0.438
	42	151	-14.90	-0.32	0.64	-1.58	0.94	0.616
	56	151	-17.38	-0.02	0.68	-1.36	1.32	0.980
	70	144	-19.00	-0.72	0.70	-2.11	0.67	0.308
	84	147	-19.97	0.22	0.62	-1.00	1.44	0.721
	112	146	-21.35	-0.56	0.64	-1.82	0.70	0.384
	140	145	-22.50	-0.15	0.59	-1.31	1.01	0.801
	168	145	-23.32	0.12	0.58	-1.02	1.25	0.838

@ nominal visits OC

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

Source Integrated Clinical Study Report Panel 19, p58

Table 2.6.8. Study 99022 - Proportion of Patients with >50% Reduction in MADRS Total Score (FAS, OC)

Treatment	Day @	MADRS >=50% Reduction n	%	Estimated Difference to CIT % points	95% Confidence Limits Lower % points	Upper % points	p-value (Fisher)
CIT	7	2	1.2				
	14	18	10.9				
	28	51	31.1				
	42	75	48.1				
	56	95	62.1				
	70	101	69.2				
	84	114	80.3				
	112	112	78.3				
	140	116	84.1				
	168	123	91.1				
ESC	7	6	3.7	-2.5	-5.8	0.8	0.164
	14	18	11.5	-0.6	-7.4	6.3	1.000
	28	43	27.9	3.2	-6.8	13.2	0.542
	42	86	57.0	-8.9	-20.0	2.3	0.138
	56	100	66.2	-4.1	-14.9	6.6	0.475
	70	101	70.1	-1.0	-11.5	9.6	0.899
	84	113	76.9	3.4	-6.0	12.9	0.567
	112	120	82.2	-3.9	-13.0	5.3	0.461
	140	124	85.5	-1.5	-9.8	6.9	0.744
	168	127	87.6	3.5	-3.7	10.7	0.440

@ nominal visits OC

Source Integrated Clinical Study Report Panel 21, p61

Table 2.6.9. Study 99022 - Proportion of Patients with MADRS Total Score < 12 (FAS, OC)

Treatment	Day @	MADRS <= 12 n	%	Estimated Difference to CIT % points	95% Confidence Limits Lower % points	Upper % points	p-value (Fisher)
CIT	7	2	1.2				
	14	10	6.1				
	28	34	20.7				
	42	59	37.8				
	56	79	51.6				
	70	82	56.2				
	84	96	67.6				
	112	100	69.9				
	140	109	79.0				
	168	111	82.2				
ESC	7	5	3.1	-1.9	-5.0	1.2	0.272
	14	17	10.8	-4.8	-10.8	1.3	0.159
	28	31	20.1	0.6	-8.3	9.5	1.000
	42	61	40.4	-2.6	-13.5	8.3	0.726
	56	87	57.6	-6.0	-17.2	5.2	0.302
	70	87	60.4	-4.3	-15.6	7.1	0.477
	84	93	63.3	4.3	-6.6	15.3	0.460
	112	105	71.9	-2.0	-12.5	8.5	0.796
	140	113	77.9	1.1	-8.5	10.6	0.885
	168	121	83.4	-1.2	-10.1	7.6	0.874

@ nominal visits OC

Source Integrated Clinical Study Report Table 24, p170

Table 2.6.10. Study 99022 - Ancova of MADRS Single Items (FAS, FINAL)

Item No.	Treatment Group	Change from Baseline	Difference to CIT	SE	p-value
01 APPARENT SADNESS	CIT	-2.41			
	ESC	-2.60	-0.19	0.11	0.081
02 REPORTED SADNESS	CIT	-2.40			
	ESC	-2.54	-0.14	0.11	0.207
03 INNER TENSION	CIT	-2.19			
	ESC	-2.11	0.08	0.12	0.464
04 REDUCED SLEEP	CIT	-2.00			
	ESC	-2.02	-0.02	0.13	0.894
05 REDUCED APPETITE	CIT	-1.57			
	ESC	-1.74	-0.17	0.10	0.101
06 CONCENTR.DIFFICULTIES	CIT	-2.12			
	ESC	-2.27	-0.15	0.11	0.172
07 LASSITUDE	CIT	-2.26			
	ESC	-2.44	-0.18	0.11	0.108
08 INABILITY TO FEEL	CIT	-2.29			
	ESC	-2.32	-0.03	0.11	0.784
09 PESSIMISTIC THOUGHTS	CIT	-2.23			
	ESC	-2.21	0.02	0.10	0.835
10 SUICIDAL THOUGHTS	CIT	-1.16			
	ESC	-1.31	-0.15	0.08	0.053

Source Integrated Clinical Study Report Panel 26, p67

Table 2.6.11. Study 99022 - CGI Severity score per visit (FAS, OC)

		Observed Cases (OC)					
Treatment Group	Day e	n	Mean	SD	Median	Minimum	Maximum
CIT	0	174	4.33	0.75	4.00	2	6
	7	172	4.11	0.85	4.00	2	6
	14	165	3.73	0.93	4.00	1	6
	28	164	3.32	0.97	3.00	1	6
	42	156	2.86	1.03	3.00	1	7
	56	153	2.59	0.97	3.00	1	5
	70	146	2.40	0.92	2.00	1	5
	84	142	2.18	0.90	2.00	1	4
	112	143	2.08	0.95	2.00	1	5
	140	138	1.90	0.90	2.00	1	4
	168	135	1.74	0.88	2.00	1	5
ESC	0	165	4.16	0.79	4.00	2	6
	7	163	3.93	0.84	4.00	2	6
	14	157	3.59	0.88	4.00	2	5
	28	155	3.16	0.94	3.00	1	5
	42	151	2.87	0.99	3.00	1	6
	56	151	2.56	1.10	2.00	1	5
	70	144	2.28	1.08	2.00	1	5
	84	147	2.20	1.05	2.00	1	5
	112	146	2.01	0.95	2.00	1	5
	140	145	1.90	0.97	2.00	1	5
	168	145	1.65	0.92	1.00	1	5

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Source Integrated Clinical Study Report Table 31, p181

Table 2.6.12. Study 99022 - Treatment Difference of the Adjusted Mean Changes from Baseline of CGI Severity

(FAS, OC)

Treatment Group	Day @	n	Least Squares Mean	Difference to CIT	SE	95% Confidence Limits Lower	Upper	p-value
CIT	7	172	-0.23					
	14	165	-0.64					
	28	164	-1.02					
	42	156	-1.44					
	56	153	-1.74					
	70	146	-1.90					
	84	142	-2.12					
	112	143	-2.24					
	140	138	-2.43					
	168	135	-2.57					
ESC	7	163	-0.29	-0.07	0.06	-0.19	0.06	0.297
	14	157	-0.70	-0.06	0.08	-0.21	0.09	0.432
	28	155	-1.15	-0.14	0.08	-0.30	0.03	0.112
	42	151	-1.44	-0.00	0.09	-0.18	0.18	0.995
	56	151	-1.76	-0.02	0.10	-0.23	0.18	0.839
	70	144	-2.05	-0.15	0.10	-0.35	0.05	0.147
	84	147	-2.13	-0.01	0.09	-0.19	0.17	0.894
	112	146	-2.30	-0.07	0.09	-0.24	0.11	0.459
	140	145	-2.44	-0.02	0.08	-0.18	0.15	0.849
	168	145	-2.67	-0.10	0.08	-0.26	0.07	0.250

@ nominal visits OC

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

Source Integrated Clinical Study Report Table 35, p191

Table 2.6.13. Study 99022 - Treatment Difference of the Adjusted Mean Changes from Baseline of Hamilton Anxiety Total (FAS, OC)

Treatment Group	Day @	n	Least Squares Mean	Difference to CIT	SE	95% Confidence Limits Lower	Upper	p-value
CIT	14	165	-6.53					
	28	163	-10.09					
	56	153	-14.40					
	168	135	-19.70					
ESC	14	157	-6.97	-0.44	0.58	-1.59	0.71	0.454
	28	154	-10.39	-0.31	0.60	-1.50	0.88	0.608
	56	150	-14.48	-0.07	0.66	-1.37	1.22	0.910
	168	145	-19.42	0.29	0.62	-0.93	1.50	0.643

@ nominal visits OC

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

Source Integrated Clinical Study Report Table 43, p204

s22

2.7 Results of the comparative RCTs

The results of each of the primary and secondary efficacy outcomes are presented in Table 2.6.1-2.6.4. Each of the trials individually supports the claim of therapeutic equivalence of escitalopram and citalopram.

A meta-analysis of the three eight week trials 99003, MD01 and MD03 has been conducted by the Lundbeck biostatistical department and the results are shown in Table 2.7.1. There were no significant differences between ESC and CIT in any of the endpoints at 8 weeks except for the MADRS score observed cases.

A separate meta-analysis of the three trials has been published (Gorman, Korotzer & Su, 2002)[12]. The results are shown in Table 2.7.1a. The results are broadly similar except for the MADRS score at 8 weeks which is reported to be -0.7 instead of -1.08. Lundbeck biostatistical department assert the value obtained by their analysis is the correct value. Nevertheless both values support the lack of statistical difference between the two treatments.

A summary of the endpoints from the trials is shown in Table 2.7.2.

Tables 2.7.1. Pooled analysis of the three 8-week studies (Lundbeck biostatistical department)

Esc vs Cit	Mean (95%CI)	p-value
MADRS		
MADRS OC	-1.23 (-2.44 -0.02)	0.0457
MADRS LOCF	-1.08 (-2.26 0.11)	0.0744
CGI-S		
CGI-S OC	-0.14 (-0.31 0.02)	0.0790
CGI-S LOCF	-0.12 (-0.27 0.03)	0.1236
CGI-I		
CGI-I OC	-0.1 (-0.24 0.05)	0.2048
CGI-I LOCF	-0.06 (-0.2 0.09)	0.4504
HAMD 17		
HAMD 17 OC	-0.72 (-1.82 0.38)	0.1981
HAMD 17 LOCF	-0.64 (-1.67 0.4)	0.2274
HAMD 24		
HAMD 24 OC	-0.78(-2.23 0.66)	0.2883
HAMD 24 LOCF	-0.67 -2.02 0.69	0.3342

Source Lundbeck biostatistical department, Copenhagen

Tables 2.7.1a. Pooled analysis of the three 8-week studies (Gorman 2002)

	PBO	ESC	CIT	ESC – CIT^
Female (%)	64	67	61	
Mean age (years)	42	41	42	
Mean weight pounds (kg)	176 (80)	170 (77)	174 (79)	
Baseline MADRS mean (SD)	29 (4.6)	28.7 (4.5)	28.9 (4.6)	
Results				
MADRS (LOCF)				
MADRS Week 1	-3.8	-4.7*#	-3.7	-1.0
MADRS Week 2	-6.6	-7.8*	-7.2	-0.6
MADRS Week 4	-9.4	-11.0*	-10.2	-0.8
MADRS Week 6	-10.3	-13.0*	-12.0*	-1.0
MADRS Week 8	-11.2	-13.8*	-13.1*	-0.7
MADRS in severe patients (>30) (LOCF)				
MADRS (severe) Week 1	-4.2	-5.5*	-4.3	-1.2
MADRS (severe) Week 2	-7.4	-9.0*	-7.9	-1.1
MADRS (severe) Week 4	-10.4	-12.2*	-11.3	-0.9
MADRS (severe) Week 6	-11.7	-14.7*	-12.8	-1.9
MADRS (severe) Week 8	-12.2	-16.2*	-14.3	-1.9
CGI-I (LOCF)				
CGI-I Week 1	3.5	3.3*	3.4	-0.1
CGI-I Week 2	3.2	3.0*	3.1	-0.1
CGI-I Week 4	2.9	2.6*	2.7*	-0.1
CGI-I Week 6	2.8	2.4*	2.5*	-0.1
CGI-I Week 8	2.7	2.4*	2.3*	0.1

** p<0.05 for active treatment vs PBO*
 # p<0.05 for ESC vs CIT
Source Gorman, J.M., Korotzer, A., Su G., 2002, Efficacy comparison of escitalopram and citalopram in the treatment of major depressive disorder Pooled analysis of placebo-controlled trials', CNS Spectrums,. Vol ,7 suppl 1, pp 40-44.[12]
^ Our calculations

Table 2.7.2. Efficacy outcomes of RCTs

Outcome - ITT-LOCF	*Study 99003*	*Study MD01*	*Study MD02*	*Study 99002 (24 week study)*
***Primary**: MADRS – Least squares mean change from baseline to final assessment (95%CI).*	*PBO -12.11 (-13.44 - 10.78)* *CIT -13.59 (-14.91 -12.27)* *ESC -15.02 (-16.35 - 13.69)*	*PBO -9.4 (-11.1; -7.7)* *CIT -12.0 (-13.8;-10.2)* *ESC 10mg -12.8 (-14.3;-11.3)* *ESC 20mg -13.9 (-15.5; -12.3)*	*PBO -11.2 (-13.0; -9.4)* *CIT -13.0 (-14.8;-11.2)* *ESC -12.9 (-14.7;-11.1)*	
***Primary**: MADRS – Difference in mean change from baseline to final assessment (95%CI).*	*CIT-PBO -1.48 (-3.30;0.33) p=0.109* *ESC-PBO -2.91 (-4.73;-1.09) p= 0.002*	*CIT-PBO -2.5 (-5.0;-0.1) p=0.0414* *ESC 10mg-PBO -3.9 (-6.2;-1.7) p= 0.0007* *ESC 20mg-PBO -4.6 (-6.9;-2.4) p= <0.0001*	*CIT-PBO -1.9 (-4.4; 0.7) p=0.151* *ESC-PBO -1.4 (-3.9; 1.0) p=0.251*	
***Primary**: MADRS – the development of the total scores during the 24 weeks of double-blind treatment using repeated measures analysis on the observed cases (OC) data.*				*The upper confidence limit for the slope parameter for escitalopram minus the slope parameter for citalopram was 0.119, which is smaller than the 0.375 required for non-inferiority. Escitalopram was thus at least as efficacious as citalopram.*
***Secondary:** Proportion (%) of patients with at least 50% reduction of the MADRS total score from baseline at (responders) (95%CI). LOCF*	*PBO 43.5 (35.5 -51.7)* *CIT 49.7(41.7 -57.7)* *ESC 61.3 (53.1-69.0)*			

Secondary: *Difference in proportion (%) of patients with at least 50% reduction of the MADRS total score from baseline at (responders) (95%CI). LOCF*	*CIT-PBO 6.2 (-4.9;17.2) p=0.308* *ESC-PBO 17.8 (6.8;28.7) p= 0.002*			
Secondary: *Proportion (%) of patients with at MADRS score ≤12 per (complete remission) (95%CI). LOCF*	*PBO 40.9 (33.1;49.1)* *CIT 39.6 (32.0;47.7)* *ESC 50.3 (42.2;58.4)*			
Secondary: *Difference in proportion (%) of patients with at MADRS score ≤12 per (complete remission) (95%CI). LOCF*	*CIT-PBO -1.3 (-12.2;9.6) p=0.819* *ESC-PBO 9.4 (-1.6;20.5) p=0.110*			
CGI-S scale– Change from baseline to Week 8 LOCF (95%CI).	*PBO -1.41 (-1.59;-1.22)* *CIT -1.56 (-1.74;-1.37)* *ESC -1.79 (-1.98;-1.61)*	*PBO -0.8 (-1.0; -0.6)* *CIT -1.2 (-1.4;-1.0)* *ESC 10mg -1.3 (-1.5;-1.1)* *ESC 20mg -1.4 (-1.6; -1.2)*	*PBO -1.1 (-1.3; -0.9)* *CIT -1.5 (-1.7;-1.3)* *ESC -1.3 (-1.5;-1.1)*	
CGI-S scale– Difference in mean change from baseline to Week 8 LOCF (95%CI).	*CIT-PBO -0.15 (-0.40;0.10) p=0.245* *ESC-PBO -0.38 (-0.64;-0.13) p=0.003*	*CIT-PBO -0.3 (-0.6;-0.0) p=0.0266* *ESC 10mg-PBO -0.5 (-0.8;-0.3) p= 0.0002* *ESC 20mg-PBO -0.6 (-0.8;-0.3) p= <0.0001*	*CIT-PBO -0.4 (-0.7;-0.0) p=0.024* *ESC -PBO -0.1 (-0.4;0.2) p=0.439*	
CGI-I Adjusted change from baseline to visit of CGI-I score LOCF (95%CI).	*PBO 2.51 (2.33;2.68)* *CIT 2.20 (2.02;2.38)* *ESC 2.08 (1.90;2.26)*	*PBO 3.0 (2.8; 3.2)* *CIT 2.6 (2.4; 2.8)* *ESC 10mg 2.5 (2.3; 2.7)* *ESC 20mg 2.4 (2.2; 2.6)*	*PBO 2.6 (2.4; 2.8)* *CIT 2.3 (2.1; 2.5)* *ESC 2.5 (2.3; 2.7)*	

CGI-I Difference in adjusted change from baseline in CGI I scores (95%CI). LOCF	*CIT-PBO -0.31 (-0.55;-0.06) p=0.014* *ESC-PBO -0.43 (-0.67;-0.18) p=0.001*	*CIT-PBO -0.4 (-0.7;-0.1) p=0.0140* *ESC 10mg-PBO -0.5 (-0.8;-0.2) p= 0.0007* *ESC 20mg-PBO -0.6 (-0.8;-0.3) p= <0.0001*	*CIT-PBO -0.4 (-0.6;-0.1)p=0.0160* *ESC-PBO -0.1 (-0.4;0.2) p= 0.466*	
Proportion (%) of patients with a CGI-I score ≤2 (95%CI). LOCF	*PBO 54.5 (46.3;62.6)* *CIT 64.8 (56.8;72.2)* *ESC 72.9 (65.2;79.7)*			
Difference in proportion (%) of patients with CGI-I score ≤2 (95%CI). LOCF	*CIT-PBO 10.2 (-0.6;21.0) p=0.067* *ESC-PBO 18.4 (7.8;28.9) p=0.001*			
***HAMD**– Change from baseline to Week 8 (95%CI).*		*PBO -7.6 (-9.1; -6.1)* *CIT -9.9 (-11.6;-8.2)* *ESC 10mg -10.2 (-11.6;-8.8)* *ESC 20mg -11.7 (-13.2; -10.2)*	*PBO -9.6 (-11.2; -8.0)* *CIT -11.4 (-12.9;-9.9)* *ESC -10.4 (-12.0;-8.8)*	
***HAMD**– Difference in mean change from baseline to Week 8 (95%CI).*		*CIT-PBO -2.2 (-4.3;-0.0) p=0.0518* *ESC 10mg-PBO -3.3 (-5.2;-1.3) p= 0.0014* *ESC 20mg-PBO -4.1 (-6.0;-2.1) p= <0.0001*	*CIT-PBO -2.0 (-4.2;0.1) p=0.068* *ESC-PBO -0.7 (-2.8; 1.4) p=0.506*	

HAMD Depressed mood item *– Change from baseline to Week 8 LOCF (95%CI).*		*PBO -0.9 (-1.1; -0.7)* *CIT -1.4 (-1.6;-1.2)* *ESC 10mg -1.3 (-1.5; -1.1)* *ESC 20mg -1.4 (-1.6; -1.2)*	*PBO -1.1 (-1.3; -0.9)* *CIT -1.3 (-1.5;-1.1)* *ESC -1.2 (-1.4; -1.0)*	
HAMD – Depressed mood item *- Difference in mean change from baseline to Week 8 LOCF (95%CI).*		*CIT-PBO -0.5 (-0.7; -0.2) p=0.0005* *ESC 10mg-PBO -0.5 (-0.7; -0.2) p=0.0006* *ESC 20mg-PBO -0.5 (-0.8; -0.3) p= <0.0001*	*CIT-PBO -0.4 (-0.7; -0.0) p=0.024* *ESC-PBO -0.1 (-0.4; 0.2) p=0.439*	
Secondary				***24 week study***
MADRS *- Change from baseline to each assessment in total score.*				*Figure 2.7.4. There were numerically larger improvements for the escitalopram group than for the citalopram group in the LOCF dataset. There were no statistically significant differences between treatment groups in the adjusted mean change from baseline at any time point.*
MADRS *- Change from baseline to final assessment in total score (Day 168)*				*CIT -23.44* *ESC -23.32 Difference to CIT =0.12 (95%CI: -10.2-1.25) p=0.838*

MADRS *- Proportion of patients with at least a 50% reduction of the total score (responders) from baseline per visit.*				*See Figure 2.7.5. There was no statistically significant difference between treatment groups in the proportion of responders at any time point (OC or LOCF).*
MADRS *- Proportion of patients with at least a 50% reduction of the total score from baseline to final assessment (responders) (Day 168)*				*CIT 91.1* *ESC 87.6 Difference to CIT =3.5 (95%CI: -3.7-10.7) p=0.440*
MADRS *- Proportion of patients with a total score =12 (remitters) per visit*				*See Figure 2.7.6. There was no statistical difference between treatment groups in the proportion of remitters at any time point (OC or LOCF).*
MADRS *- Proportion of patients with a total score ≤12 (remitters) at final assessment (Day 168).*				*CIT 82.2* *ESC 83.4 Difference to CIT =-1.2 (95%CI: -10.1-7.6) p=0.874*
MADRS *- Change from baseline to final assessment of all single items*				*See Figure 2.7.7. For escitalopram, borderline statistical superiority was found for item 10 (suicidal thoughts, p = 0.053). In all, eight of the 10 items were numerically superior for escitalopram (items 1, 2, 4, 5, 6, 7, 8, and 10).*

CGI-S - *score per visit*				*See Figure 2.7.8.*
CGI-S *- Change from baseline to visit of score*				*See Figure 2.7.9.*
CGI-S *- Change from baseline to final assessment in score*				*CIT –2.57* *ESC –2.67 Difference to CIT =-0.10 (95%CI: -0.26-0.07) p=0.874*
HAMA *scores per visit*				*See Figure 2.7.10.*
HAMA - *scores at final assessment*				*CIT –19.70* *ESC –19.42 Difference to CIT =-0.29 (95%CI: -0.93-1.50) p=0.643*

ESC: Escitalopram, CIT: Citalopram, ITT: Intention to treat, HAMD: Hamilton Depression Rating Scale, CGI: Clinical Global Impressions, AE: Adverse Event, ECG: electocardiogram, PBO: Placebo, OC: Observed cases, LOCF: Last observation carried forward, Analysis of covariance: ANOVA: Analysis of variance, CMH:Cochran-Mantle-Haenszel APRS: All Patients Randomised Set – all patients randomised in the study. APTS: All patients Treated set – all randomised patients who took at least one dose of double-blind study product., FAS – all randomised patients who took at least one dose of double blind study product and who had at least one post-baseline assessment of the MADRS total score

2.8 Interpretation of the results of the comparative RCTs

Categorisation of escitalopram

Based on the data summarised in this submission, escitalopram offers modest advantages over citalopram in offering equivalent efficacy and safety with a significant improvement in the MADRAS scores at week 1. However, we have not attempted to quantify this potential benefit for escitalopram.

On this basis, a cost minimisation approach has been adopted for this submission based on 10mg of escitalopram being equivalent to 20mg of citalopram.

Analysis of the three 8-week trials was conducted by comparing the treatments escitalopram and citalopram with PBO. For the majority of efficacy endpoints, escitalopram was numerically better than citalopram, although the difference did not achieve statistical difference.

A pooled analysis of the three eight week studies did not detect any difference in the MADRS or CGI-I scores except for an statistically greater reduction at weeks 1 and 6 in MADRS for patients on ESC. The early response compared with CIT is likely to benefit patients.

A long term head to head RCT of ESC and CIT (99022) further confirmed the equivalence of the two treatments.

The equivalence of escitalopram and citalopram can be clearly seen by inspection of the graphs of the change in the MADRS score for Study 99003 and MD01.

Figure 2.8.1 shows the mean change in MADRS total scores from baseline by Week (LOCF) in Study 99003. It can be clearly seen that the decrease in the MADRS score with escitalopram was greater at each week than both citalopram and escitalopram. While the difference between escitalopram and PBO was statistically significant at week 8 (p=0.002), the difference between citalopram and escitalopram did not reach statistical significance.

These results are similar for Study MD01. In this study, escitalopram (20mg/day) and citalopram (40mg/day) were very similar with escitalopram (10mg/day) being less efficacious. The mean change from baseline in the MADRS scores at each week using the LOCF dataset are presented graphically in Figure 2.8.2.

These results demonstrate graphically that the efficacy of escitalopram is equivalent to citalopram.

In the LOCF by visit analyses, both the 10 mg/day and 20 mg/day escitalopram treatment groups showed significant improvements compared to placebo as early as the second week of treatment (p=0.0256 and p=0.0311, respectively) and continued to show this difference at every visit through the end of Week 8. Citalopram produced numerically greater improvement than placebo at Week 2 and all subsequent visits, and the difference achieved statistical significance at Week 8.

The efficacy of escitalopram is further supported by the statistically significant improvement in the CGI severity in two out of the three studies. Once again, the extent of improvement was equivalent for escitalopram and citalopram.

The efficacy of escitalopram has been shown for both the fixed 10 and 20mg daily dosage regimen as well as for the flexible 10 to 20mg daily dose regimen. Escitalopram is effective in both moderate and severe depression, but there is some evidence that the 20mg dose may be preferred in treating those with more severe depression. The efficacy of escitalopram has been demonstrated in different settings. Escitalopram was effective both in Europe and in the United States, and both in secondary care psychiatric practice and in a primary care setting.

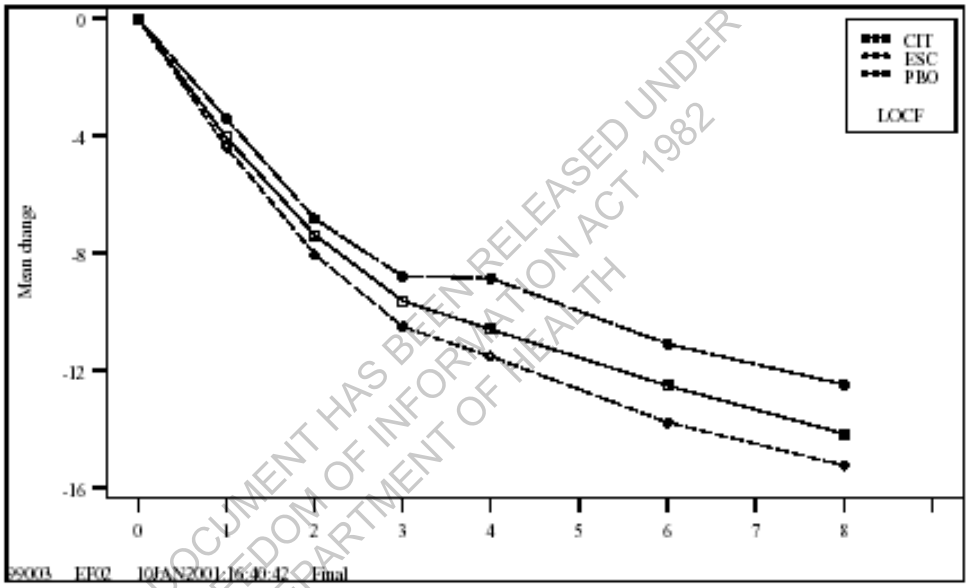
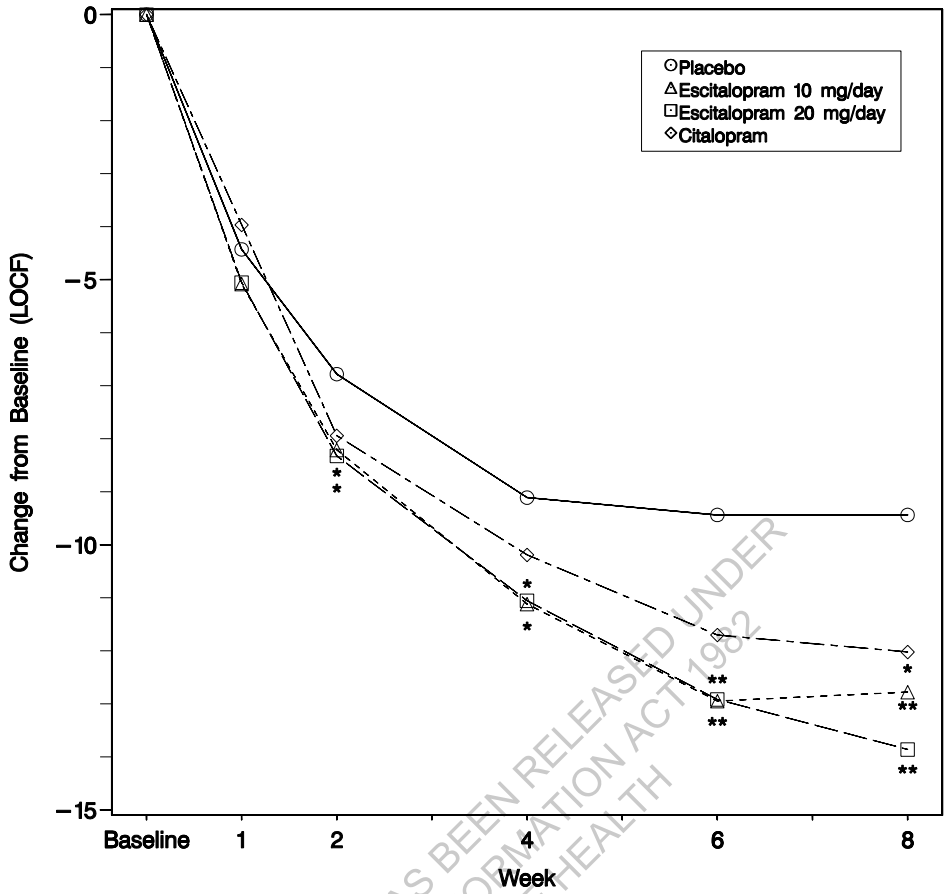


Figure 2.8.1 Study 99003. Mean Change in MADRS Total Scores from Baseline by Week (LOCF)



*p<0.05 for comparison versus placebo; ** p<0.001 for comparison versus placebo

Figure 2.8.2 Study MD01. Mean Change in MADRS Total Scores from Baseline by Week (LOCF)

Relative Potency of escitalopram vs citalopram

The trials indicate that a 10mg per day dose of escitalopram is equivalent to 20mg of citalopram.

In the flexible dose trial 99003, dosage could be increased at Week 4. By week 8, the mean capsules per day was PBO, 1.5; citalopram 1.4 (28.4mg) and citalopram 1.4 (14mg) (See below). The similarity in titration rates confirm that escitalopram (10mg) and citalopram (20mg) were of similar potency.

Table 2.8.1. Study 99003. Mean daily dose at Week 8

	PBO	CIT		ESC	
	capsules/day	*capsules/day*	*mg/day*	*capsules/day*	*mg/day*
Mean	*1.5*	*1.4*	*28.4*	*1.4*	*14.0*
N	*140*	*151*	*151*	*147*	*147*
Std Dev	*0.50*	*0.49*	*9.84*	*0.49*	*4.85*

The titration rates were similar in Study MD02, albeit higher. By week 8, the mean capsules per day for PBO was 1.9; citalopram 1.8 (35.3mg) and citalopram 1.4 (17.6mg) (See below).

Table 2.8.2. Study MD01. Mean daily dose at Week 8

	PBO	CIT		ESC	
	capsules/day	*capsules/day*	*mg/day*	*capsules/day*	*mg/day*
Mean	*1.9*	*1.8*	*35.3*	*1.8*	*17.6*
N	*107*	*105*	*105*	*98*	*98*
Std Dev	*0.30*	*0.39*	*7.8*	*0.41*	*4.14*

A long term head to head RCT of ESC and CIT (99022) further confirmed the equivalence of the two treatments.

Explanation for the failure of MD01 to show a therapeutic effect for escitalopram and 40mg citalopram

This study did not distinguish a significant drug/placebo difference for either escitalopram or citalopram over 8 weeks on the primary outcome measure of the MADRS change score in the LOCF analysis of the ITT population.

At the end of week 8, the escitalopram and citalopram treatment groups exhibited numerically greater improvement on the MADRS than the placebo group, but the differences were not statistically significant in the LOCF analyses. The treatment by centre interaction for this

analysis was not statistically significant (p=0.106). For the OC analyses at week 8, the MADRS score for escitalopram was significantly improved (p=0.032) versus placebo. Citalopram treated patients also showed significantly greater improvement (p=0.050) than placebo in the week 8 OC analysis.

Because of the lack of statistical separation from placebo for the reference antidepressant citalopram and for escitalopram on the primary efficacy measure (LOCF), this study must be regarded as a failed study with a population and design which for some reason was unable to properly test efficacy. However, on the basis of the OC analysis and the statistically significant finding when the small centres were reweighted according to the number of patients included, escitalopram was significantly better than placebo on the primary measure; small-centre variability could therefore explain the failure of the study. Thus there is clearly supportive evidence in this study for the efficacy of escitalopram.

Social Anxiety Disorder

2A.4 Assessment of the measures taken by investigators to minimise bias in the comparative randomised trials

Evidence for the use of escitalopram in the treatment of social anxiety disorder is derived from study 99270 which was published by Lader et al, 2004.

2A.4.1 Overview

Randomisation, adequacy of follow-up and blinding of the individual studies are described in **Table 9**.

Table 9 Randomisation, adequacy of follow-up and blinding of study 99270

Randomisation§	Adequacy of follow-up₸	Blinding*
3	3	2

§The randomisation procedures were assessed using the categories in Appendix D of the guidelines, as follows:

1. No details of randomisation were reported, or the method used was inadequate (e.g. randomisation according to the day of the week, even/odd medical record numbers).
2. An insecure randomisation method was used, where clinical staff could possibly learn of the treatment assignment (e.g. randomisation sequence kept in the clinical area and open/unblinded trial; treatment assignment kept in consecutive "sealed" envelopes and open/unblinded trial).
3. A secure randomisation method was used, where the randomisation sequence was kept away from the clinical area and administered by staff not directly involved in patient care (e.g. randomisation performed at a separate site available through a toll-free number or by the pharmacy department after the decision had been made to enter the subject in the trial).

₸ Adequacy of follow-up was assessed using the categories in Appendix D of the guidelines, as follows:

1. There were significant numbers of drop-outs with no assessment of trial outcomes in the subjects who dropped-out, and drop out rates differed between treated and control groups.
2. There were some drop-outs with no assessment of trial outcome(s) in the subjects who dropped-out, and drop-out rates were (approximately) equivalent in treated and control groups.
3. Trial outcomes(s) were assessed in all treated and control subjects who did not withdraw from the trial.

* Blinding was assessed using the categories in Appendix D of the guidelines, as follows:

1. There was an inadequate attempt (or no attempt) to blind observer(s), and the measurement technique was subject to observer bias (e.g. blood pressure measurement with standard sphygmomanometer, measurement of vertebral height on X-ray, quality of life instrument.
2. The observer(s) were kept fully blinded to treatment assignment, or the measurement technique was not subject to observer bias (e.g. measurement of bone mineral density or survival)

2A.4.2 Randomisation

Patients who met the selection criteria at the screening and baseline visits were assigned to treatment in a 1:1:1:1:1 ratio to escitalopram 5 mg, escitalopram 10 mg, escitalopram 20 mg, paroxetine or placebo according to a randomisation code generated by H.Lundbeck A/S. At each centre, patients were consecutively assigned the lowest randomisation number available. Block randomisation ensured that equal numbers of patients entered each treatment group.

2A.4.3 Adequacy of follow-up

The following data analysis sets were defined in the Statistical Analysis Plan:

- all-patients-randomised set (APRS): all randomised patients
- all-patients-treated set (APTS): all patients in the APRS who took at least one dose of double-blind study product
- full-analysis set (FAS): all patients in the APTS who had at least one valid post-baseline assessment of the primary efficacy variable (LSAS total score)
- per-protocol set (PPS): all randomised patients who had no major protocol violations, who received double-blind study product at least up to Week 4, and who had at least one assessment of the LSAS total score at or after Week 4.

A summary of the position disposition is provided in **Table 10**.

Table 10 Summary of patient disposition: study 99270

	PBO		PAR		ESC5		ESC10		ESC20		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients randomised (APRS)	166		169		167		168		170		840	
Patients treated (APTS)	166		169		167		167		170		839	
Patients completed	112	(67.5)	119	(70.4)	122	(73.1)	107	(64.1)	116	(68.2)	576	(68.7)
Patients withdrawn	54	(32.5)	50	(29.6)	45	(26.9)	60	(35.9)	54	(31.8)	263	(31.3)
Efficacy data sets												
Full analysis set (FAS)	165		167		166		164		163		825	
Per Protocol Set (PPS)	160		147		156		151		150		764	

PBO = placebo, PAR = paroxetine, ESC5 = escitalopram 5 mg, ESC10 = escitalopram 10 mg, ESC20 = escitalopram 20 mg

2A.4.4 Blinding

Patients and observer(s) were fully blinded with regard to treatment assignment.

The study products were encapsulated and active treatments and placebo were indistinguishable from one another with respect to appearance, shape, taste, and smell.

The study product for each week was packed into wallet cards containing 10 capsules (3 extra capsules per week) and wallet cards were packed into visit cartons. A patient kit consisted of 10 visit cartons with study product for 24 weeks of double-blind treatment (one capsule daily), and 2 visit cartons with placebo treatment (one capsule daily) for the run-out

period (Weeks 25 and 26). The wallet cards were labelled with the randomisation number, re-test (or expiry) date, packaging batch number, and visit number.

Three sets of sealed envelopes containing treatment details for each patient in the double-blind treatment period were prepared. One copy was kept by each of the following: the International Clinical Research–Mood Disorder Department at H.Lundbeck A/S; International Safety and Pharmacovigilance (ISPV) at H.Lundbeck A/S; and the investigator or pharmacist.

All envelopes were collected at the end of the study. The randomisation code was to be broken only in an emergency situation in order to give the patient optimal treatment. The randomisation code was not broken for any patient during the study.

2A.5 Characteristics of the comparative randomised trials

2A.5.1 Trial design

The trial design is summarised in **Table 11**.

Table 11 Trial design: study 99270

Design	Centres	Dose of escitalopram	Dose of comparators	Duration
Multicentre, multinational, fixed-dose, double-blind, randomised, placebo-controlled, active-reference	47 centres in 11 countries	5 mg/day, 10 mg/day, or 20 mg/day	placebo	• 1-week, single-blind, placebo lead-in period; • 24 weeks of double-blind treatment; • 2-weeks, single-blind, placebo run-out period
			paroxetine 20 mg/day	

In Australia, the recommended dose for escitalopram is 10 mg daily and the maximum dose is 20 mg daily. The recommended dose for paroxetine is 20 mg daily, however, patients may receive a maximum of 50 mg daily. Therefore, the trial includes the recommended doses of escitalopram and paroxetine, but does not include the maximum dose of paroxetine. The trial also included escitalopram 5 mg daily which is lower than the recommended dose of 10 mg and would normally be used in the elderly, patients with hepatic impairment and patients with genetic polymorphism.

2A.5.2 Inclusion and exclusion criteria

The inclusion and exclusion criteria are included in **Table 12**.

Table 12 Inclusion and exclusion criteria: study 99270

Inclusion criteria	Exclusion criteria
• 18–65 years of age; • outpatients; • primary diagnosis of generalised SAD; according to DSM-IV criteria; • total score ≥70 on the Liebowitz Social Anxiety Scale (LSAS); • demonstrable fear and avoidance traits in at least four social situations; • a score ≥5 on one or more of the Sheehan Disability Scale (SDS) subscales; • otherwise healthy based on physical examination, medical history, anamesis, ECG and the results of blood biochemistry and haematology tests; and • willing to attend study appointments in the correct time windows.	• another Axis I disorder designated the primary diagnosis within the previous 6 months; • were receiving (or planning to initiate) formal psychotherapy and/or cognitive behaviour therapy; • alcohol or drug abuse problem as defined in DSM-IV; • baseline MADRS total score ≥18; • body dysmorphic disorder, as defined in DSM-IV; • Axis II Cluster B diagnosis: antisocial personality disorder, borderline personality disorder, histrionic personality, or narcissistic personality disorder; • MDD, panic disorder (patients with panic attacks not due to panic disorder could be included), or obsessive-compulsive disorder (OCD) as defined in DSM-IV; • schizophrenia, as defined in DSM-IV, or any other psychotic disorder, or had a history thereof; • female patient of child-bearing potential who was pregnant or breastfeeding or without adequate contraception (adequate defined as oral/systemic contraception); • eating disorders (bulimia or anorexia), as defined in DSM-IV; • mental retardation or other cognitive disorder; • used any of the disallowed therapies within the specified time periods; • history of lack of response to previous treatment for SAD with an SSRI; • known hypersensitivity to citalopram, escitalopram, or paroxetine; • at significant risk of suicide or had a score ≥5 on item 10 on the MADRS; • history of severe drug allergy or hypersensitivity; • clinical laboratory values outside normal ranges and considered clinically significant; • disease that could interfere with the assessments of safety, tolerability, or efficacy; • Serious illness of: liver or renal insufficiency, cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurological, infectious, neoplastic, or metabolic disturbance. • unlikely to comply with the clinical study protocol or unsuitable for any other reason(s)

2A.5.3 Baseline demographics

The baseline demographics of the patients in the studies are included in **Table 13**.

Table 13 Baseline demographics: study 99270

	PBO		PAR		ESC5		ESC10		ESC20	
Sex										
Female n (%)	85	(51.2)	91	(53.8)	83	(49.7)	96	(57.5)	90	(52.9
Age										
Mean	37		37.4		36.3		37.2		37	
SD	11.8		11.4		10.9		11.3		10.6	
Race										
Caucasian n (%)	166	(100)	166	(98.2)	166	(99.4)	165	(98.8)	170	(100)

PBO = placebo, PAR = paroxetine, ESC5 = escitalopram 5 mg, ESC10 = escitalopram 10 mg, ESC20 = escitalopram 20 mg

The baseline characteristics of patients in the study are similar to those treated for social anxiety disorder in Australia as 53% of patients in the study were female and 56% of patients in Australia with social anxiety disorder are female (AIHW, 1998:10). The mean age in the study was 37 years old and the age of patients in Australia with anxiety disorders is also highest around the 35-44 and 45-54 age brackets (AIHW, 1998:11). Therefore, Australian patients treated for social anxiety disorder are unlikely to differ from patients treated in the clinical trial.

2A.6 Analysis of the comparative randomised trials

2A.6.1 Efficacy outcomes

The primary efficacy endpoint was the change from baseline to Week 12 (LOCF) in LSAS total score.

The secondary efficacy endpoints included:

- change from baseline to each visit in LSAS total score,
- proportion of patients with a ≥50% reduction in LSAS total score from baseline to visit,
- change from baseline to last assessment in LSAS subscale (fear/anxiety, avoidance) scores,
- change from baseline to final assessment in LSAS single items,
- CGI-S score per visit,
- change from baseline to each visit in CGI-S score,
- CGI-I score per visit,
- proportion of patients with a CGI-I score ≤2 per visit,
- proportion of patients with a CGI-S score ≤2 per visit,
- change from baseline to each visit in SDS items 1-3 score.

Details of the scales and measures used as efficacy outcomes are as follows:

Liebowitz Social Anxiety Scale (LSAS)

The LSAS is designed to assess SAD through evaluation of fear and avoidance in social situations. The LSAS includes 24 items of which 13 describe performance situations and 11 describe social interactional situations. Each item is rated for fear (scale 0 to 3) and avoidance (0 to 3). The LSAS has four subscales: fear/social, avoidance/social, fear/performance, and avoidance/performance. Total scores for fear, avoidance, and LSAS total scores are calculated by summing the scores.

Clinical Global Impression Scale (CGI)

The CGI consists of two subscales:

- Clinical Global Impression Improvement Scale (CGI-I) – This single-item rating scale evaluates a patient's total improvement from baseline on a defined 7-point scale regardless of whether the improvement is related to the study product. The investigator (physician) or trained rater rated the patient from 1 (*very much improved*) to 7 (*very much worse*).
- Clinical Global Impression Severity Scale (CGI-S) – This single-item rating scale evaluates a patient's severity of illness on a defined 7-point scale based on the investigator's total clinical experience with patients. The investigator (physician) or trained rater rated the patient from 1 (*normal*, *not at all ill*) to 7 (*extremely ill*).

Sheehan Disability Scale (SDS)

The SDS is a 3-item scale to measure disability/functional impairment. The items address the impact of symptoms of SAD on work, social life, and family life over the previous 7 days. The rating was based upon an interview with the patient.

2A.6.2 Safety outcomes

Safety outcomes included reporting of adverse events (serious and non-serious) including consideration of intensity, causality and outcome; laboratory tests, ECG, vital signs and discontinuation emergent signs and symptoms (DESS).

2A.7 Results of the comparative randomised trials

2A.7.1 Efficacy results

The mean changes from baseline in LSAS total score, adjusted for centre and baseline LSAS are shown in **Table 14**.

Table 14 Treatment difference of the adjusted mean changes from baseline in LSAS total score (FAS LOCF Weeks 12 and 24): study 99270

			Least Squares Estimates		Difference to placebo				
Treatment Group	Week	n	Mean	SE	Mean	SE	95% CI lower	95% CI upper	p-value
PBO	12	165	-29.48	1.95					
	24	165	-34.04	2.17					
PAR	12	167	-39.31	1.96	-9.83	2.66	-15.04	-4.61	0.000
	24	167	-45.87	2.17	-11.82	2.95	-17.62	-6.03	0.000
ESC5	12	166	-38.66	1.95	-9.18	2.66	-14.40	-3.95	0.001
	24	166	-44.51	2.16	-10.46	2.96	-16.27	-4.66	0.000
ESC10	12	164	-34.55	1.96	-5.07	2.68	-10.32	0.18	0.059
	24	164	-41.50	2.17	-7.45	2.97	-13.29	-1.62	0.012
ESC20	12	163	-39.79	1.97	-10.31	2.67	-15.56	-5.06	0.000
	24	163	-49.13	2.19	-15.09	2.97	-20.92	-9.25	0.000

PBO = placebo; PAR = paroxetine; ESC5 = escitalopram 5 mg; ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg

At 12 weeks, escitalopram 5 mg and 20 mg and paroxetine were statistically superior to placebo while the difference for escitalopram 10 mg did not reach statistical significance. However at 24 weeks, all active treatment groups were statistically significantly superior to placebo. The inferior result of escitalopram 10 mg appears to be consistent throughout the study which appears to have been an anomaly in this study as in a placebo-controlled study of escitalopram for the treatment of SAD, the magnitude of results with escitalopram 10 mg after 12 weeks of treatment was similar to that achieved in this study after 24 weeks of treatment (Kasper et al, 2005).

The adjusted mean changes from baseline in LSAS avoidance, fear and anxiety, CGI-S and the adjusted means for CGI-I are shown in **Tables 15-18**, respectively. The pattern of results was similar to the results for LSAS total scores.

Table 15 Treatment difference of the adjusted mean changes from baseline in LSAS avoidance (FAS LOCF Weeks 12 and 24): study 99270

			Least Squares Estimates		Difference to placebo				
Treatment Group	Week	n	Mean	SE	Mean	SE	95% CI lower	95% CI upper	p-value
PBO	12	164	-15.45	1.03					
	24	164	-17.88	1.13					
PAR	12	166	-20.05	1.03	-4.59	1.40	-7.34	-1.84	0.001
	24	166	-23.46	1.13	-5.57	1.54	-8.59	-2.56	0.000
ESC5	12	166	-19.89	1.02	-4.43	1.40	-7.18	-1.68	0.002
	24	166	-22.86	1.12	-4.98	1.54	-7.99	-1.96	0.001
ESC10	12	162	-17.91	1.03	-2.45	1.41	-5.22	0.32	0.082
	24	162	-21.08	1.13	-3.20	1.55	-6.24	-0.16	0.039
ESC20	12	162	-20.54	1.04	-5.09	1.41	-7.85	-2.23	0.000
	24	162	-25.01	1.14	-7.13	1.55	-10.17	-4.10	0.000

PBO = placebo; PAR = paroxetine; ESC5 = escitalopram 5 mg; ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg

Table 16 Treatment difference of the adjusted mean changes from baseline in LSAS fear and anxiety (FAS LOCF Weeks 12 and 24): study 99270

			Least Squares Estimates		Difference to placebo				
Treatment Group	Week	n	Mean	SE	Mean	SE	95% CI lower	95% CI upper	p-value
PBO	12	164	-13.82	0.99					
	24	164	-16.19	1.09					
PAR	12	166	-19.14	0.99	-5.31	1.35	-7.96	-2.67	0.000
	24	166	-22.36	1.10	-6.17	1.49	-9.10	-3.25	0.000
ESC5	12	166	-18.77	0.98	-4.94	1.35	-7.58	-2.30	0.000
	24	166	-21.72	1.09	-5.53	1.49	-8.45	-2.60	0.000
ESC10	12	163	-16.62	0.99	-2.80	1.35	-5.46	-0.14	0.039
	24	163	-20.22	1.09	-4.03	1.50	-6.97	-1.09	0.007
ESC20	12	163	-19.21	1.00	-5.39	1.35	-8.04	-2.74	0.000
	24	163	-24.13	1.10	-7.94	1.50	-10.88	-5.00	0.000

PBO = placebo; PAR = paroxetine; ESC5 = escitalopram 5 mg; ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg

Table 17 Treatment difference of the adjusted mean changes from baseline in CGI Severity (FAS LOCF Weeks 12 and 24): study 99270

			Least Squares Estimates		Difference to placebo				
Treatment Group	Week	n	Mean	SE	Mean	SE	95% CI lower	95% CI upper	p-value
PBO	12	165	-1.14	0.09					
	24	165	-1.35	0.10					
PAR	12	167	-1.63	0.09	-0.49	0.12	-0.73	-0.24	0.000
	24	167	-1.96	0.10	-0.61	0.14	-0.88	-0.34	0.000
ESC5	12	166	-1.69	0.09	-0.55	0.12	-0.79	-0.31	0.000
	24	166	-1.86	0.10	-0.50	0.14	-0.78	-0.23	0.000
ESC10	12	163	-1.49	0.09	-0.35	0.12	-0.59	-0.11	0.004
	24	163	-1.79	0.10	-0.44	0.14	-0.71	-0.16	0.002
ESC20	12	162	-1.69	0.09	-0.55	0.12	-0.79	-0.31	0.000
	24	162	-2.12	0.10	-0.77	0.14	-1.04	-0.50	0.000

PBO = placebo; PAR = paroxetine; ESC5 = escitalopram 5 mg; ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg

Table 18 Treatment difference of the adjusted means of CGI Improvement (FAS LOCF Weeks 12 and 24): study 99270

			Least Squares Estimates		Difference to placebo				
Treatment Group	Week	n	Mean	SE	Mean	SE	95% CI lower	95% CI upper	p-value
PBO	12	165	2.66	0.08					
	24	165	2.51	0.09					
PAR	12	167	2.24	0.08	-0.42	0.11	-0.64	-0.19	0.000
	24	167	2.14	0.09	-0.37	0.12	-0.61	-0.14	0.002
ESC5	12	166	2.28	0.08	-0.37	0.11	-0.59	-0.15	0.001
	24	166	2.12	0.09	-0.40	0.12	-0.63	-0.16	0.001
ESC10	12	164	2.45	0.08	-0.21	0.11	-0.43	0.01	0.067
	24	164	2.30	0.09	-0.21	0.12	-0.45	0.02	0.078
ESC20	12	162	2.33	0.08	-0.32	0.11	-0.55	-0.10	0.005
	24	162	2.03	0.09	-0.48	0.12	-0.72	-0.25	0.000

PBO = placebo; PAR = paroxetine; ESC5 = escitalopram 5 mg; ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg

As study 99270 was designed to demonstrate superiority of escitalopram versus placebo and not equivalence between escitalopram and paroxetine, post-hoc analyses were conducted in order to demonstrate the therapeutic equivalence of escitalopram and paroxetine. This was performed by verifying that the true difference (primary outcome) between two therapies is unlikely to be outside a predetermined range (-Δ to +Δ). The values of Δ represent the

difference that would be considered clinically significant (±10 for the L-SAS). Thus, if the 95% confidence interval of the difference lies entirely between ±Δ, then the equivalence is demonstrated. All differences and confidence intervals were calculated using an ANOVA model of the change from baseline of a given scale including the corresponding baseline as covariate and center and treatment group as factor. **Table 19** gives the confidence interval for the primary and secondary endpoints of the trials. As all the confidence intervals for the LSAS total score range within –10;10 on the primary endpoint (L-SAS total score), we can conclude that escitalopram 5 mg and 10 mg are equivalent to paroxetine 20 mg.

Table 19 Confidence intervals for differences in clinical efficacy (escitalopram 5 mg and escitalopram 10 mg vs paroxetine 20 mg (week 24): sudy 99270

	ESC 5 vs PAR 20			ESC 10 vs PAR 20		
	Estimate	IC -	IC +	Estimate	IC -	IC +
L-SAS total score	1,80	-3,96	7,56	2,19	-3,73	8,12
L-SAS fear & anxiety	1,07	-1,88	4,03	1,23	-1,82	4,28
L-SAS avoidance	0,55	-2,47	3,57	1,03	-2,10	4,15
CGI-S	0,12	-0,16	0,41	0,07	-0,22	0,36
CGI-I	0,00	-0,21	0,22	0,04	-0,18	0,26

PBO = placebo; PAR = paroxetine; ESC5 = escitalopram 5 mg; ESC10 = escitalopram 10 mg

The same comparison with the escitalopram 20 mg arm showed that escitalopram 20 mg is significantly more efficacious than paroxetine 20 mg (**Table 20**).

Table 20 Confidence intervals for differences in clinical efficacy (escitalopram 20 mg vs paroxetine 20 mg (Week 24): Study 99270

	ESC 20 vs PAR 20		
	Estimate	IC -	IC +
L-SAS total score	-7,68	-13,43	-1,93
L-SAS fear & anxiety	-3,76	-6,72	-0,81
L-SAS avoidance	-4,10	-7,12	-1,08
CGI-S	-0,35	-0,63	-0,07
CGI-I	-0,29	-0,51	-0,08

PBO = placebo; PAR = paroxetine; ESC20 = escitalopram 20 mg

The results for other efficacy measures are shown in **Tables 21-26**.

Table 21 Proportion of patients with at least 50% reduction in LSAS total score (FAS LOCF Weeks 12 and 24): study 99270

Treatment Group	Week	LSAS ≥50% reduction N	LSAS ≥50% reduction %	Estimated difference to PBO %	95% Confidence intervals Lower %	95% Confidence intervals Upper %	p-value Fisher
PBO	12	34	20.6				
	24	47	28.5				
PAR	12	68	40.7	20.1	10.4	29.8	0.000
	24	81	48.5	20.0	9.8	30.3	0.000
ESC5	12	54	32.5	11.9	2.5	21.4	0.018
	24	78	47.0	18.5	8.3	28.8	0.001
ESC10	12	48	29.3	8.7	-0.6	18.0	0.075
	24	75	45.7	17.2	7.0	27.5	0.001
ESC20	12	64	39.3	18.7	8.9	28.4	0.000
	24	91	55.8	27.3	17.1	37.6	0.000

PBO = placebo; PAR = paroxetine; ESC5 = escitalopram 5 mg; ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg

Table 22 Differences between treatment groups in the proportion of patients with CGI-S ≤2 (FAS LOCF Weeks 12 and 24): study 99270

Treatment Group	Week	LSAS ≥50% reduction N	LSAS ≥50% reduction %	Estimated difference to PBO %	95% Confidence intervals Lower %	95% Confidence intervals Upper %	p-value Fisher
PBO	12	22	13.3				
	24	32	19.4				
PAR	12	50	29.9	16.6	7.9	25.3	0.000
	24	73	43.7	24.3	14.7	34.0	0.000
ESC5	12	48	28.9	15.6	7.0	24.2	0.001
	24	65	39.2	19.8	10.2	29.3	0.001
ESC10	12	40	24.4	11.1	2.7	19.4	0.011
	24	61	37.2	17.8	8.3	27.3	0.000
ESC20	12	44	27.0	13.7	5.1	22.2	0.002
	24	75	46.0	26.6	16.9	36.4	0.000

PBO = placebo; PAR = paroxetine; ESC5 = escitalopram 5 mg; ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg

Table 23 Differences between treatment groups in the proportion of patients with CGI-I ≤2 (FAS LOCF Weeks 12 and 24): study 99270

Treatment Group	Week	LSAS ≥50% reduction N	LSAS ≥50% reduction %	Estimated difference to PBO %	95% Confidence intervals Lower %	95% Confidence intervals Upper %	p-value Fisher
PBO	12	68	41.2				
	24	83	50.3				
PAR	12	103	61.7	20.5	9.9	31.0	0.000
	24	111	66.5	16.2	5.7	26.6	0.004
ESC5	12	101	60.8	19.6	9.1	30.2	0.000
	24	111	66.9	16.6	6.1	27.0	0.003
ESC10	12	90	54.9	13.7	3.0	24.4	0.015
	24	95	57.9	7.6	-3.1	18.4	0.185
ESC20	12	101	62.0	20.8	10.2	31.3	0.000
	24	114	69.9	19.6	9.3	30.0	0.000

PBO = placebo; PAR = paroxetine; ESC5 = escitalopram 5 mg; ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg

Table 24 Treatment difference of the adjusted mean changes from baseline in SDS work scores (FAS LOCF Weeks 12 and 24): study 99270

Treatment Group	Week	n	Least Squares Estimates Mean	Least Squares Estimates SE	Difference to placebo Mean	Difference to placebo SE	95% CI lower	95% CI upper	p-value
PBO	12	163	-1.98	0.19					
	24	163	-2.35	0.20					
PAR	12	165	-2.98	0.19	-1.01	0.26	-1.51	-0.50	0.000
	24	165	-3.54	0.20	-1.19	0.28	-1.74	-0.65	0.000
ESC5	12	166	-3.13	0.19	-1.16	0.26	-1.66	-0.65	0.000
	24	166	-3.63	0.20	-1.28	0.28	-1.82	-0.73	0.000
ESC10	12	163	-2.74	0.19	-0.77	0.26	-1.27	-0.26	0.003
	24	163	-3.28	0.20	-0.93	0.28	-1.48	-0.38	0.001
ESC20	12	163	-3.19	0.19	-1.21	0.26	-1.72	-0.71	0.000
	24	163	-3.92	0.20	-1.57	0.28	-2.11	-1.02	0.000

PBO = placebo; PAR = paroxetine; ESC5 = escitalopram 5 mg; ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg

Table 25 Treatment difference of the adjusted mean changes from baseline in SDS social score (FAS LOCF Weeks 12 and 24): study 99270

			Least Squares Estimates		Difference to placebo				
Treatment Group	Week	n	Mean	SE	Mean	SE	95% CI lower	95% CI upper	p-value
PBO	12	165	-2.53	0.18					
	24	165	-2.78	0.20					
PAR	12	167	-3.16	0.19	-0.63	0.25	-1.12	-0.14	0.012
	24	167	-3.75	0.20	-0.97	0.27	-1.50	-0.44	0.000
ESC5	12	166	-3.38	0.18	-0.85	0.25	-1.34	-0.35	0.001
	24	166	-3.88	0.20	-1.10	0.27	-1.63	-0.57	0.000
ESC10	12	164	-2.95	0.18	-0.42	0.25	-0.92	-0.08	0.098
	24	164	-3.60	0.20	-0.82	0.27	-1.36	-0.29	0.003
ESC20	12	163	-3.39	0.19	-0.86	0.25	-1.35	-0.36	0.001
	24	163	-4.28	0.20	-1.50	0.27	-2.03	-0.97	0.000

PBO = placebo; PAR = paroxetine; ESC5 = escitalopram 5 mg; ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg

Table 26 Treatment difference of the adjusted mean changes from baseline in SDS family score (FAS LOCF Weeks 12 and 24): study 99270

			Least Squares Estimates		Difference to placebo				
Treatment Group	Week	n	Mean	SE	Mean	SE	95% CI lower	95% CI upper	p-value
PBO	12	165	-1.43	0.16					
	24	165	-1.59	0.16					
PAR	12	167	-1.95	0.16	-0.52	0.22	-0.95	-0.10	0.015
	24	167	-2.34	0.16	-0.75	0.22	-1.18	-0.32	0.001
ESC5	12	166	-2.16	0.16	-0.73	0.22	-1.15	-0.31	0.001
	24	166	-2.64	0.16	-1.05	0.22	-1.49	-0.62	0.000
ESC10	12	164	-1.90	0.16	-0.47	0.22	-0.90	-0.05	0.030
	24	164	-2.26	0.16	-0.67	0.22	-1.11	-0.24	0.002
ESC20	12	163	-2.02	0.16	-0.59	0.22	-1.02	-0.17	0.006
	24	163	-2.65	0.16	-1.06	0.22	-1.49	-0.62	0.000

PBO = placebo; PAR = paroxetine; ESC5 = escitalopram 5 mg; ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg

s22

Generalised Anxiety Disorder

Evidence for the use of escitalopram in the treatment of generalised anxiety disorder is derived from two clinical studies: study SCT-MD-20 which includes paroxetine as a comparator and study 99815 which includes paroxetine as an active reference. Details of these studies are provided in **Table 30**.

Table 30 Generalised anxiety disorder studies

Number	Study
SCT-MD-20	A double-blind comparison of escitalopram and paroxetine in the treatment of generalized anxiety disorder. **Published as:** Bielski RJ, Bose A and Chang C-C. A double-blind comparison of escitalopram and paroxetine in the long-term treatment of generalized anxiety disorder. Annals of Clinical Psychiatry 2005; 17(2):65-9.
99815	A double-blind, randomised, placebo-controlled trial comparing the efficacy and safety of fixed dosages of escitalopram with that of placebo in patients with generalised anxiety disorder. **Published as**: Baldwin DS, Huusom AKT and Mæhlum E. Escitalopram and paroxetine in the treatment of generalised anxiety disorder. British Journal of Psychiatry 2006, 189:264-272.

2B.4 Assessment of the measures taken by investigators to minimise bias in the comparative randomised trials

2B.4.1 Overview

Randomisation, adequacy of follow-up and blinding of the studies is described in **Table 31**.

Table 31 Randomisation, adequacy of follow-up and blinding of the studies SCT-MD-20 and 99815

Study	Randomisation§	Adequacy of follow-up₮	Blinding*
SCT-MD-20	3	3	2
99815	3	3	2

§The randomisation procedures were assessed using the categories in Appendix D of the guidelines, as follows:

1. No details of randomisation were reported, or the method used was inadequate (e.g. randomisation according to the day of the week, even/odd medical record numbers).
2. An insecure randomisation method was used, where clinical staff could possibly learn of the treatment assignment (e.g. randomisation sequence kept in the clinical area and open/unblinded trial; treatment assignment kept in consecutive "sealed" envelopes and open/unblinded trial).
3. A secure randomisation method was used, where he randomisation sequence was kept away from the clinical area and administered by staff not directly involved in patient care (e.g. randomisation performed at a separate site available through a toll-free number or by the pharmacy department after the decision had been made to enter the subject in the trial).

₮ Adequacy of follow-up was assessed using the categories in Appendix D of the guidelines, as follows:

1. There were significant numbers of drop-outs wi h no assessment of trial outcomes in the subjects who dropped-out, and drop out rates differed between treated and control groups.
2. There were some drop-outs with no assessment of trial outcome(s) in the subjects who dropped-out, and drop-out rates were (approximately) equivalent in treated and control groups.
3. Trial outcomes(s) were assessed in all treated and control subjects who did not withdraw from the trial.

* Blinding was assessed using the categories in Appendix D of the guidelines, as follows:

1. There was an inadequate attempt (or no attempt) to blind observer(s), and the measurement technique was subject to observer bias (e.g. blood pressure measurement with standard sphygmomanometer, measurement of vertebral height on X-ray, quality of life instrument.
2. The observer(s) were kept fully blinded to treatment assignment, or the measurement technique was not subject to observer bias (e.g. measurement of bone mineral density or survival)

2B.4.2 Randomisation

Study SCT-MD-20

Each study site was provided with drug supplies corresponding to a sequence of patient randomisation numbers. The first patient who met eligibility criteria at the end of the one-week, single-blind placebo lead-in period and entered the study was assigned the first number in the sequence and each subsequent patient entered was assigned a sequential patient randomisation number.

Study 99815

Patients who met the selection criteria at the screening and baseline visits were assigned to 12 weeks of double-blind treatment in a 1:1:1:1:1 ratio of escitalopram 5 mg, escitalopram 10 mg, escitalopram 20 mg, paroxetine 20 mg and placebo according to a randomisation code generated by H.Lundbeck A/S. At each centre, patients were consecutively assigned to the lowest randomization number available.

2B.4.3 Adequacy of follow up

Study SCT-MD-20

The patient populations were as follows:

- Randomised population: all patients randomised in the study.
- Safety population: all patients who received at least one dose of double-blind study medication.
- Intent-to-Treat population: all patients in the safety population with at least one post-baseline efficacy assessment on the Hamilton rating scale for Anxiety (HAMA).

Patient disposition is shown in **Table 32**.

Table 32 Summary of patient disposition: study SCT-MD-20

	Escitalopram	Paroxetine	Total
Safety population, n	61	62	123
ITT population, n	60	61	121
Completers, n (%)	39 (63.9%)	33 (53.2%)	72 (58.5%)
Total withdrawn for any reason	22 (36.1%)	29 (46.8%)	51 (41.5%)
Reasons for discontinuation			
Adverse event	4 (6.6%)	12 (22.6%)	18 (14.6%)
Insufficient therapeutic response	0	2 (3.2%)	2 (1.6%)
Protocol violation	4 (6.6%)	2 (3.2%)	6 (4.9%)
Withdrawal of consent	4 (6.6%)	5 (8.1%)	9 (7.3%)
Lost to follow-up	7 (11.5%)	6 (9.7%)	13 (10.6%)
Other reasons	3 (4.9%)	0	3 (2.4%)

Study 99815

The following analysis sets were defined:

- all-patients-randomised set (APRS) which included all randomised patients
- all-patients-treated set (APTS) which included all patients in the APRS who took at least one dose of double-blind study product
- full-analysis set (FAS) which included all patients in the APTS who had at least one valid post-baseline assessment of the primary efficacy variable
- all-patients-completed set (APCS) which included all patients in the FAS who completed 12 weeks of double-blind treatment
- per-protocol set (PPS) which included all patients in the FAS who received double-blind study product for at least 4 weeks, who had at least one valid assessment of the HAMA total score at or after the Week 4 assessment, and who had no major protocol violations.

All efficacy analyses were conducted on the FAS. If appropriate, additional efficacy analyses were conducted on other analysis data sets. Safety analyses (except analyses of DESS) were conducted on the APTS.

Patient disposition is shown in **Table 33**.

Table 33 Summary of patient disposition: study 99815

	PBO		PAR		ESC5		ESC10		ESC20		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients randomised (APRS)	139		140		134		136		133		682	
Patients treated (APTS)	139		139		134		136		133		681	
Patients completed	124	(89.2)	113	(81.3)	117	(87.3)	118	(86.8)	111	(83.5)	583	(85.6)
Patients withdrawn	15	(10.8)	26	(18.7)	17	(12.7)	18	(13.2)	22	(16.5)	98	(14.4)
Efficacy data sets												
Full analysis set (FAS)	138		136		134		134		132		674	
Per Protocol Set (PPS)	128		122		122		122		116		610	

PBO = placebo, PAR = paroxetine, ESC5 = escitalopram 5 mg, ESC10 = escitalopram 10 mg, ESC20 = escitalopram 20 mg

2B.4.3 Blinding

Study SCT-MD-20

Patients and observer(s) were fully blinded with regard to treatment assignment.

A list of patient randomisation numbers and the corresponding assigned treatment was generated by Forest Laboratories Department of Biostatistics and retained in electronic form.

A hard copy was retained by the Department of Drug Safety Surveillance in a secure locked area.

The study products were encapsulated and active treatments and placebo were indistinguishable from one another with respect to appearance, shape, taste, and smell.

Active treatment and placebo were packed in blisters in a manner which allowed for an increase of dosage of escitalopram to 20 mg and paroxetine to 50 mg, if necessary. The double-blind medication was labeled with a tear-off panel that, once opened, revealed the treatment assignment. This tear-off panel was placed in the patient's case report form. In the case of emergency, the tear-off panel could be opened, or Forest Laboratories telephoned, to reveal the patient's treatment assignment. However, it was required that attempts be made to discuss with the medical monitor prior to unblinding, and if the blind was broken, Forest Laboratories was to have been notified immediately.

Study 99815

Patients and observer(s) were fully blinded with regard to treatment assignment.

The active treatments and their matching placebo treatments (capsules) were indistinguishable from one another since they were identical in appearance, shape, taste, and smell. The study products were packed into wallet cards containing treatment (7 + 3 extra capsules) for 1 week.

The patient-kit for 14 weeks of double-blind treatment (including washout) thus contained 14 wallet cards. The wallet cards were labelled with the randomisation number, re-test (or expiry) date, packaging batch number, and visit number.

Three sets of sealed envelopes containing coded details for each patient in the double-blind treatment period were prepared. One copy was kept by each of the following: the study director, ISPV, and the investigator or pharmacist. All envelopes were collected at the end of the study.

The randomisation code was to be broken only in an emergency situation in order to give the patient optimal treatment. The randomisation code was not broken for any patient during the study.

2B.5 Characteristics of the comparative randomised trials

2B.5.1 Trial design

The trial designs are summarised in **Table 34**.

Table 34 Trial designs

Study	Design	Centres	Dose of escitalopram	Dose of comparators	Duration
SCT-MD-20	Multicentre, randomised, double-blind, comparative, flexible-dose, parallel group	8 US sites	10-20 mg/day	paroxetine 20-50 mg/day	• 1-week, single-blind, placebo lead-in period; • 24 weeks of double-blind treatment; • 2-weeks, double-blind, down-titration
99815	Multinational, multicentre, randomised, double-blind, parallel-group, placebo-controlled, active-reference, fixed dose	64 centres in 10 countries	Fixed doses of 5 mg, 10 mg, 20 mg/day	paroxetine 20 mg/day	• 1-week, single-blind, placebo lead-in period; • 12 weeks of double-blind treatment; • 2-week washout period

Study SCT-MD-20 uses doses which are approved in Australia for the treatment of generalised anxiety disorder of escitalopram 10-20 mg per day and paroxetine 20-50 mg per day.

Study 99815 includes the recommended doses of escitalopram and paroxetine, but does not include the maximum dose of paroxetine. The trial also included escitalopram 5 mg daily which is lower than the recommended dose of 10 mg and would normally be used in the elderly, patients with hepatic impairment and patients with genetic polymorphism.

2B.5.2 Inclusion and exclusion criteria

The inclusion and exclusion criteria are included in **Tables 35** and **36**, respectively.

Table 35 Inclusion criteria

	Study SCT-MD-20	Study 99815
Population	Male and female outpatients	Male and female outpatients
Age	18-65 years	18-65 years
Diagnosis	DSM-IV of generalised anxiety disorder	DSM-IV of generalised anxiety disorder
HAMA at baseline	≥18	≥20
HAMA items	--	Score ≥2 on both HAMA item 1 (anxious mood) and item 2 (tension) at screening and baseline
MADRS		≤16
Covi Anxiety vs Raskin Depression	Covi Anxiety Scale score > Raskin Depression Scale score	--
Medical	Otherwise healthy	Otherwise healthy

Table 36 Exclusion criteria

Study SCT-MD-20	Study 99815
• Women who are pregnant or breastfeeding during the study and women of childbearing potential not practicing a reliable method of birth control; • Met DSM-IV criteria for: o Bipolar disorder, o Schizophrenia or any psychotic disorder, o Obsessive compulsive disorder, o Mental retardation or any pervasive developmental disorder or Cognitive disorder; • Principle diagnosis meeting DSM-IV criteria for another Axis I disorder; • Met DSM-IV criteria for substance abuse or dependence (other than nicotine) within past six months; • Psychotic features; • Suicide risk or serious suicide attempt within the last year; • Any malignancy (other than excised basal cell carcinoma), any clinically significant haematological, endocrine, cardiovascular (including rhythm disorder), renal, hepatic, gastrointestinal or neurological (including epilepsy) disease; • Systolic blood pressure >180 mm Hg or <90 mm Hg or diastolic blood pressure >105 mm Hg or <50 mm Hg at screening and baseline visits; • Prohibited medication within specified time periods; • Require ECT or received ECT within 3 months prior to study entry	• Females of child-bearing potential who had positive pregnancy tests at screening visit, were without adequate contraception or were pregnant or breastfeeding; • Met DSM-IV-TR criteria for, or it was considered the predominant disorder within previous 6 months: o Major depressive disorder, o Panic disorder, o Social anxiety disorder, o Posttraumatic stress disorder, o Bipolar disorder, o Obsessive compulsive disorder, o Eating disorders, o Body dysmorphic disorder, o Substance abuse disorder, o Any personality disorders that could jeopardise the evaluation of the treatment for primary GAD, o Any psychotic disorders or history thereof; • Risk of suicide or had score >3 points on item 10 of MADRS or serious suicide attempt within past year; • Unstable serious illness and/or serious sequelae of: liver or renal insufficiency, or cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurological, infectious, neoplastic or metabolic disturbance; • Prohibited therapies within specified time periods; • Required ECT or had received ECT within 6 months prior to screening

Table 36 Exclusion criteria (continued)

Study SCT-MD-20	Study 99815
• Previously failed to respond to adequate trial of any two SSRIs • Plan to initiate or terminate, or initiated or terminated behaviour therapy or psychotherapy within 3 months prior to study entry; • Positive test for alcohol, prohibited or illicit drugs on urine drug screen; • In opinion of investigator might not be suitable for the study.	• Previously failed to respond to an adequate dose and duration of treatment with SSRIs and/or SNRIs; • Receiving cognitive behaviour therapy, cognitive therapy or problem-solving treatment or planned to initiate such therapy; • History of severe drug allergy or hypersensitivity, or a known allergy or hypersensitivity to citalopram, escitalopram and/or paroxetine; • In investigator's opinion unable or unlikely to follow study protocol.

2B.5.3 Baseline characteristics

The baseline demographics of the patients in the studies SCT-MD-20 and 99815 are included in **Table 37** and **38**, respectively.

Table 37 Baseline demographics: study SCT-MD-20

	Escitalopram (N = 61)		Paroxetine (N = 62)		Total (N =123)	
Sex						
Female n (%)	34	(55.7)	42	(67.7)	76	(61.8)
Age						
Mean	36.8		37.4		37.1	
Min, Max	20, 62		19, 61		19, 62	
Race						
Caucasian n (%)	44	(72.1)	49	(79.0)	93	(75.6)

Table 38 Baseline demographics: study 99815

	PBO		PAR		ESC5		ESC10		ESC20		Total	
Sex												
Female n (%)	93	(66.9)	84	(60.4)	78	(58.2)	91	(66.9)	92	(69.2)	438	(64.3)
Age												
Mean	41.8		41.7		40.7		41.8		41		41.4	
SD	11.6		12.0		11.9		12.8		12.2		12.1	
Race												
Caucasian n (%)	138	(99.3)	137	(98.6)	132	(98.5)	135	(99.3)	131	(98.5)	673	(98.8)

PBO = placebo, PAR = paroxetine, ESC5 = escitalopram 5 mg, ESC10 = escitalopram 10 mg, ESC20 = escitalopram 20 mg

The baseline characteristics of patients in the studies are similar to those treated for generalised anxiety disorder in Australia as 62% of patients in study SCT-MD-20 and 64% in study 99815 were female and 62% of patients in Australia with generalised anxiety disorder are female (AIHW, 1998:10). The mean age in study SCT-MD-20 was 37 years old and in study 99815 was 41 years and the age of patients in Australia with anxiety disorders is also highest around the 35-44 and 45-54 age brackets (AIHW, 1998:11). Therefore, Australian

patients treated for generalised anxiety disorder are unlikely to differ from patients treated in the clinical trial.

2B.6 Analysis of the comparative randomised trials

2B.6.1 Efficacy outcomes

The efficacy outcomes are described in **Table 39**.

Table 39 Efficacy outcomes

Endpoints	Study SCT-MD-20	Study 99815
Primary efficacy	Change from baseline in HAMA total score at week 24 (LOCF).	Change from baseline to Week 12 in HAMA total score, using the last observation carried forward (LOCF) approach.
Secondary efficacy	• Change from baseline in HAMA psychic anxiety subscale score, • CGI score, and • Change from baseline in CGI-S score.	• change from baseline to each visit in HAMA total score • change from baseline to each visit in HAMA psychic anxiety subscale score • change from baseline to each visit in HAMA somatic anxiety subscale score • change from baseline to each visit in HAMA score for item 1 (anxious mood) • change from baseline to each visit in HAMA score for item 2 (tension) • proportion of responders (patients with a ≥50% reduction in HAMA total score from baseline to each visit) • proportion of remitters (patients with a HAMA total score ≤9 per visit) • change from baseline to each visit in HAD anxiety score • CGI-S score per visit • change from baseline to each visit in CGI-S score • CGI-I score per visit • proportion of responders (patients with a CGI-I score ≤2 per visit) • change from baseline to each visit in SDS (work, family life, social life) scores
Other	Changes from baseline in: • HAD anxiety score, • HAD depression score, • Covi score, • Raskin score, • HAMD score, • HAMD anxiety subscale score, • HAMA somatic anxiety subscale score, • HAMA anxiety item, • HAMA tension item, and • QoL score.	Proportion of remitters (patients with a HAMA total score ≤7 per visit) was included as an exploratory efficacy endpoint.

Details of the scales and measures used as efficacy outcomes are as follows:

HAMA

This 14-item scale rated the patient's level of anxiety based on feelings of anxiousness, tension and depression; any phobias, sleep disturbance, or difficulty in concentrating; the presence of genitourinary, cardiovascular, respiratory, autonomic or somatic symptoms; and the interviewer's assessment of the patient's appearance and behaviour during the interview.

Each item is scored on a 5 point scale with 0 reflecting no symptoms and 4 reflecting symptoms of maximum severity.

HAMA items and subscale scores were also considered as shown above.

Clinical Global Impressions (CGI)

Refer to 2A.6.1.

Hospital anxiety and depression scale (HAD)

The HAD is completed by the patient and comprises two subscales, one of which measures depression (D-scale) and the other measures anxiety (A-scale). Each subscale is made up of 7 items, with 4 possible response alternatives (scores of 0 to 3) in each instance. The D-scale consists of HAD items 1, 3, 5, 8, 10, 11, and 13, and the A-scale consists of HAD items 2, 4, 6, 7, 9, 12, and 14. Patients are required to indicate the response that most accurately reflects the way they have felt over the last few days. Scores for the depression and anxiety subscales are summed separately.

Covi Anxiety Scale score

The Covi Anxiety Scale measures the intensity of anxiety symptomatology through evaluation of three general items (anxiety perceived by the examiner in the patient's verbal report, anxiety perceived in the patient's behavior, and intensity of somatic complaints reported by the patient).

Raskin Depression Scale score

The Raskin Depression Scale rates depression severity. It explores the extent to which an individual demonstrates depression on three subscales (rated 1-5): verbal self-report, behaviour and secondary symptoms of depression. Scores range from 3-15, with higher scores indicating greater severity.

Hamilton Depression Rating Scale (HAMD)

This scale rated the patient's depressed state based on feelings of depression, guilt, suicidality, anxiety, agitation, helplessness, hopelessness, worthlessness; or

depersonalisation/derealisation, their level of insight, their patterns of insomnia, loss of interest in work and other activities, weight loss, hypochondriasis, psychomotor retardation; or the presence of paranoid, obsessive compulsive, genital, or somatic symptoms; and diurnal variation in the presence of symptoms.

Each item was scored on a 3, 4 or 5 point scale with 0 reflecting no symptoms and higher scores reflecting increased symptom severity.

Certain subitems were also considered as described above.

Quality of Life Questionnaire (QoL)

This is a 16-item patient-rated questionnaire, derived from the Quality of Life, Enjoyment and Satisfaction Questionnaire. Patients answered questions based on their satisfaction during the previous two weeks regarding mood, health, activities of daily living and interpersonal relationships on a 5-point scale. Unlike other efficacy ratings, higher scores on this scale reflect improved function.

s22

2B.7 Results of the comparative randomised trials

2B.7.1 Efficacy results

Results are presented separately for studies 99270 and 99815 and as a meta-analysis of the two sets of results.

Study SCT-MD-20

Efficacy results are show in **Table 40**.

Table 40 Efficacy results: study SCT-MD-20 (ITT, LOCF)

Outcome measure	Change or timing	Escitalopram	Paroxetine	LSMD (95% CI)	p-value
HAMA	Week 24 - baseline	-15.3	-13.3	1.90 (-0.54, 4.35)	0.125
HAMA psychic anxiety	Week 24 - baseline	-9.0	-7.3	1.38 (-0.10, 2.86)	0.068
CGI-S	Week 24 - baseline	-2.1	-1.8	0.28 (-0.14, 0.70)	0.190
CGI-I	Week 24	1.8	2.1	0.32 (-0.08, 0.72)	0.114
HAD anxiety subscale	Week 24 - baseline	-5.5	-6.1	0.46 (-1.14, 2.05)	0.572
HAD depression subscale	Week 24 - baseline	-4.1	-2.5	0.83 (-0.71, 2.37)	0.288
Covi scale	Week 24 - baseline	-4.8	-3.8	0.84 (-0.06, 1.73)	0.067
Raskin scale	Week 24 - baseline	-1.3	-1.1	0.11 (-0.43, 0.65)	0.685
HAMD	Week 24 – baseline	-6.6	-5.9	0.46 (-1.32, 2.24)	0.610
HAMD anxiety subscale	Week 24 – baseline	-3.1	-2.9	0.24 (-0.50, 0.99)	0.515
HAMD somatic anxiety subscale	Week 24 - baseline	-6.4	-6.0	0.60 (-0.54, 1.75)	0.299
HAMA anxiety item	Week 24 – baseline	-1.7	-1.6	0.22 (-0.11, 0.56)	0.189
HAMA tension item	Week 24 – baseline	-1.8	-1.5	0.29 (-0.08, 0.66)	0.127
QoL	Week 24 – baseline	10.2	7.5	-2.58 (-6.63, 1.46)	0.209

As can be seen in the above table, there were no significant differences between escitalopram and paroxetine for any of the efficacy measures.

Study 99815

Results for the primary efficacy analysis, change in HAMA total score from baseline to week 12 (LOCF) are shown in **Table 41**.

Table 41 Mean change from baseline to week 12 in HAMA total score (FAS, LOCF): study 99815

			Least Squares Estimates		Difference to placebo				
Treatment Group	Week	n	Mean	SE	Mean	SE	95% CI lower	95% CI upper	p-value
PBO	12	138	-14.20	0.66					
PAR	12	136	-14.71	0.67	-0.51	0.93	-2.33	1.32	0.585
ESC5	12	134	-15.49	0.67	-1.29	0.93	-3.13	0.54	0.165
ESC10	12	134	-16.76	0.68	-2.56	0.94	-4.40	-0.73	0.006
ESC20	12	132	-16.35	0.68	-2.15	0.94	-3.99	-0.31	0.022

PBO = placebo; PAR = paroxetine; ESC5 = escitalopram 5 mg; ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg

Escitalopram 10 mg and escitalopram 20 mg were statistically significant to placebo at endpoint whereas results for paroxetine 20 mg and escitalopram 5 mg were not statistically significant to placebo.

The mean HAMA total scores decreased steadily from baseline to week 12 in all treatment groups. In the LOCF analysis, separation of active treatment from placebo was statistically significant from week 8 onwards for 10 and 20 mg escitalopram. An exploratory analysis showed that escitalopram 10 mg was significantly superior to paroxetine 20 mg at week 12.

Table 42 shows the active treatment groups that were statistically significantly superior to placebo for the secondary efficacy endpoints at each visit.

Table 42 Active treatment group with statistical superiority (p<0.05, LOCF) compared to placebo for secondary efficacy parameters: study 99815

	Week						
Secondary efficacy parameter	**1**	**2**	**4**	**6**	**8**	**10**	**12**
HAMA Total Score					ESC10 ESC20	ESC10 ESC20	ESC10 ESC20
HAMA Psychic Anxiety Subscale Score			ESC10	ESC10	ESC10	ESC10 ESC20	ESC10
HAMA Somatic Anxiety Subscale Score							ESC10 ESC20
HAMA Item 1 (Anxious Mood) Score			PAR ESC10	PAR ESC10	ESC10	ESC10	ESC10
HAMA Item 2 (Tension) Score			PAR ESC10		ESC10	ESC10	ESC10
Proportion of patients with a 50% reduction in HAMA Total Score				ESC10			
Proportion of patients with a HAMA Total Score of 9 or less					ESC10	ESC10 ESC20	
Proportion of patients with a HAMA Total Score of 7 or less					ESC10	ESC10	ESC5 ESC10 ESC20
CGI-S Scores			PAR ESC10	PAR ESC10	PAR ESC10 ESC20	ESC10 ESC20	ESC10 ESC20
CGI-I Scores		ESC10	ESC10 ESC20	ESC10 ESC20	ESC10 ESC20	ESC10 ESC20	ESC10 ESC20
Proportion of patients with a CGI-I Score of 1 or 2		ESC10	ESC10	ESC10 ESC20	ESC10	ESC10 ESC20	ESC10
HAD Anxiety Scores	-	-	-	PAR ESC5 ESC10 ESC20	-	-	ESC10 ESC20
SDS Work Scores	-	-	-	ESC10	-	-	ESC10
SDS Social Life Scores	-	-	-	PAR ESC5 ESC10	-	-	ESC5 ESC10
SDS Family Life Scores	-	-	-	PAR ESC10	-	-	PAR ESC10 ESC20

PBO = placebo; PAR = paroxetine; ESC5 = escitalopram 5 mg; ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg

In the secondary analyses at Week 12, using LOCF, escitalopram 10 mg and 20 mg were statistically significantly (p<0.05) superior to placebo in: HAMA somatic anxiety subscale score; CGI-S and CGI-I scores; HAD anxiety total score, and SDS subscale score for family

life. Furthermore, escitalopram 10 mg was statistically significantly ($p<0.05$) superior to placebo in: HAMA psychic anxiety subscale score; SDS subscale scores for work and social life ($p<0.01$); and HAMA items 1 (anxious mood) and 2 (tension) scores. Escitalopram 5 mg was statistically significantly ($p<0.05$) superior to placebo in SDS social life score. Paroxetine (20mg) was statistically significantly ($p<0.05$) more effective than placebo in SDS family life score.

In the secondary by-week analyses using LOCF, a statistically significant ($p<0.05$) separation from placebo for escitalopram 10 mg was seen from Week 2 and onwards in CGI-I score, and from Week 4 in HAMA items 1 (anxious mood) and 2 (tension) scores, HAMA psychic anxiety subscale score, and CGI-S score. Statistically significant ($p<0.05$) separation from placebo for escitalopram 20 mg was seen at Week 4 and onwards in CGI-I score, and from Week 8 and onwards in CGI-S score.

Meta-analysis of results from studies SCT-MD-20 and 99815

Results of a meta-analysis of studies SCT-MD-20 and a subset of patients from study 99815 who received recommended doses, i.e. escitalopram 10 mg treatment group and all patients treated with paroxetine 20 mg, are shown in **Table 43**. The results show that escitalopram is superior to paroxetine for the treatment of generalised anxiety disorder.

Table 43 Results of meta-analysis of studies SCT-MD-20 and 99815*

Parameter	Difference escitalopram vs paroxetine (95% CI)		p-value
HAMA total score			
End of study§	2.08 [0.62; 3.55]		0.0054
Week 12	2.12 [0.68; 3.56]		0.0040
CGI-S			
End of study§	0.31 [0.08; 0.54]		0.0074
Week 12	0.28 [0.06; 0.49]		0.0131
CGI-I			
End of study§	0.33 [0.12; 0.55]		0.0024
Week 12	0.33 [0.13; 0.54]		0.0016
	Paroxetine	**Escitalopram**	**p-value**
Responders			
End of study§	60.9%	72.7%	0.0092
Week 12	59.9%	70.6%	0.0201

*Includes all patients from study SCT-MD-20 and patients treated with paroxetine and escitalopram 10 mg from study 99815
§Week 24 for study SCT-MD-20 and week 12 for study 99815

2.8 Interpretation of the results of the comparative randomised trials

As shown in **Tables 19** and **43**, escitalopram 10 mg per day and paroxetine 20 mg per day have equivalent efficacy for the treatment of social anxiety disorder and escitalopram 10 mg had statistically significantly superior results to paroxetine 20 mg for the treatment of generalised anxiety disorder, therefore the category which best described escitalopram when considering both of these conditions is:

(b) The proposed drug is no worse than the main comparator in terms of effectiveness and toxicity.

s22

B.2 Listing of all direct randomised trials

B.2.1 Direct randomised trials: search results

Table B.2.1 (same as Table 15 in Attachment 4) and Table B.2.2 (same as Table 14 in Attachment 4) summarise the search results for direct randomised trials; the former for Escitalopram and benzodiazepine direct RCTs, the later for Escitalopram vs placebo. Table B.2.3 summarises the search results for the benzodiazepine trials using placebo as a comparator, that will become the basis of the indirect comparison between Escitalopram and the benzodiazepines. The tables presenting the results of the literature search a merged version of and B2.2 of the Guidelines.

The Escitalopram vs. placebo trials are considered direct trials where placebo is the nominated comparator and indirect for the purpose of the indirect analysis with the benzodiazepines therefore, given that they essentially the same trials, they will be presented only in Table B.2.2.

The reasons for inclusion and exclusion are presented in Tables 18 (escitalopram and benzodiazepine) and 17 (escitalopram) in Attachment 4.

Table B.2.1: Summary of identification of direct randomised trials from the literature search: Escitalopram and Benzodiazepines

	Embase and Medline	PubMed	MEIP	CCTR	ACTR	Cochr. Libr.	Lundbeck datab. + TGA	Conf. Abstr.	HTA Datab.	Hand Search.	Total
Total number of citations retrieved	1			1							2
Total number of duplicates	0										
Total number of citations reviewed for inclusion	1			1							2
Number of citations excluded after title/abstract review:	1			1							2
Not an RCT											
RCT does not include comparator											
Trial subjects are not representative of the proposed indication	1										
Number of citations excluded after full text review:											
RCT does not include comparator											
Trial subjects are not representative of the proposed indication											
Number of citations of direct randomised trials included from each database											
Number of direct randomised trials identified for inclusion in this submission	0			0							0

Abbreviations:HTA, Health Technology Assessment; RCT, Randomised controlled trial; TGA, Therapeutic Goods Administration

Table B.2.2: Summary of identification of direct and indirect randomised trials from the literature search: Escitalopram

	Embase and Medline	PubMed	MEIP	CCTR	ACTR	Cochr. Libr.	Lundbeck datab. + TGA[2]	Conf. Abstr.	HTA Datab.	Hand Search.	Total
Total number of citations retrieved	12	11	0	4	0	6	12	1	0	0	46
Total number of duplicates		7				5	8	1			21
Total number of citations reviewed for inclusion	12	4	0	4	0	1	4	0	0		25
Number of citations excluded after title/abstract review:	9	4		4		1					18

[2] Four of the study reports have corresponding publications: these are all included in the submission but are counted only once.

Not an RCT	7	2				1					10
RCT does not include comparator	2	2		2							6
Trial subjects are not representative of the proposed indication				2							2
Number of citations excluded after full text review:											
RCT does not include comparator											
Trial subjects are not representative of the proposed indication											
Number of citations of direct randomised trials included from each database	3										7
Number of direct randomised trials identified for inclusion in this submission	3	0	0	0	0	0	4	0	0	0	7

Abbreviations:HTA, Health Technology Assessment; RCT, Randomised controlled trial; TGA, Therapeutic Goods Administration.

Table B.2.3 summarise the search results for the indirect randomised trials, using placebo as the common comparator (same as Table 18 in Attachment 4). The table presenting the results of the literature search a merged version of Tables B2.1 and B2.2 of the Guidelines.

The reasons for inclusion and exclusion are presented in Table 19 for benzodiazepine in Attachment 4.

Table B.2.3: Summary of identification of indirect randomised trials from the literature search for Benzodiazepines: DSM-IV

	Embase and Medline	PubMed	MEIP[3]	CCTR	ACTR	Cochr. Libr.	Lundbeck datab. + TGA	Conf. Abstr.	HTA Datab.	Hand Search.	Total
Total number of citations retrieved	10	24	1	3	0	6	0	0	0	20	64
Total number of duplicates		3				1				0	4
Total number of citations reviewed for inclusion	10	21	1	3	0	5	0	0	0	20	60
Number of citations excluded	5	11	1	3	0	2				6	28

[3] This article has yet to be published and only access was an abstract that presented no data. This abstract is referred to in the submission but is not used extensively as it is uncertain as to what trials were utilised in the meta-analysis.

after title/abstract review:											
Not an RCT		4	1			2				5	12
RCT does not include comparator	1	7								1	9
Trial subjects are not representative of the proposed indication	4			3	0						7
Number of citations excluded after full text review:	4	10				3				14	31
RCT does not include comparator	2					0					2
Trial subjects are not representative of the proposed indication	2	10				3				14	29
Number of citations of direct randomised trials included from each database	1										1
Number of direct randomised trials identified for inclusion in this submission	1	0	0	0	0	0	0	0	0	0	1

Abbreviations:HTA, Health Technology Assessment; RCT, Randomised controlled trial; TGA, Therapeutic Goods Administration

B.2.2 Master list of trials

Table B.2.4 provides a list of the relevant trials identified in the literature search. The trials are presented for:

Escitalopram vs placebo studies

Diazepam vs placebo studies (DSM-IV diagnosed patients)

As stated in Section A there are two comparators for escitalopram in GAD:

- Placebo; and
- benzodiazepines (specifically, diazepam and oxazepam)

There are direct, comparative studies for comparator one (placebo).

For comparator two (benzodiazepines), there are no directly comparative studies of escitalopram versus placebo. In order to compare escitalopram with benzodiazepines an indirect comparison of escitalopram (Drug A) versus placebo (Drug B) and placebo (Drug B) versus diazepam (Drug C) has to be employed. The studies comparing escitalopram and placebo are listed first (as this is also escitalopram versus comparator one, placebo). The single study comparing placebo and diazepam in DSM-IV diagnosed patients is then listed.

In addition, there is a supportive study that is an open-label continuation of three of the randomised, controlled studies comparing escitalopram and placebo. While this study is non-comparative, i.e. all patients who completed the studies then received escitalopram, it provides additional information on the longer-term efficacy and safety of escitalopram in patients with GAD. Thus, this non-randomised study is included as a supportive study, in order to present the complete data on the patients initially enrolled in the randomised, controlled trials, thereby providing some supplementary information on longer term use of escitalopram.

Table B.2.4: Trials (and associated reports) presented in the submission

Trial	Reports	Included in Nov 06 Submission
Escitalopram vs placebo direct comparative randomised trials		
Escitalopram vs placebo		
SCT-MD-05	Flexible dose comparison of the safety and efficacy of Lu 26-054 (i.e. escitalopram) and placebo in the treatment of Generalised Anxiety Disorder. 24 September, 2002.	
SCT-MD-06	Flexible dose comparison of the safety and efficacy of escitalopram and placebo in the treatment of Generalised Anxiety Disorder. 24 September, 2002.	
SCT-MD-07	Flexible dose comparison of the safety and efficacy of Lu 26-054 (i.e. escitalopram) and placebo in the treatment of Generalised Anxiety Disorder. 24 September, 2002. Davidson JRT, Bose A, Korotzer A, Zheng H. Escitalopram in the treatment of generalized anxiety disorder: Double-blind, placebo controlled, flexible-dose study. *Depression and Anxiety* 2004;19(4):234-240.[1]	

Trial	Reports	Included in Nov 06 Submission
SCT-MD-31	A double-blind flexible dose comparison of escitalopram, venlafaxine XR and placebo in the treatment of Generalised Anxiety Disorder. 24 June, 2005	
99815[4]	A double-blind, randomised, placebo-controlled trial comparing the efficacy and safety of fixed dosages of escitalopram with that of placebo in patients with Generalised Anxiety Disorder. 27 May 2004. Baldwin DS, Huusom AKT, Maehlim E. Escitalopram and Paroxetine compared to placebo in the treatment of generalized anxiety disorder (GAD). 17th Congress of Neuropsychopharmacology, Sweden, October 2004 Baldwin DS, Trap Huusom AK, Mæhlum E. Escitalopram and paroxetine in the treatment of generalised anxiety disorder. British Journal of Psychiatry, 2006, 189: 264-272[2].	Yes
99769	A double-blind, randomised, placebo-controlled, multicentre, relapse-prevention trial with 20mg escitalopram in patients with Generalised Anxiety Disorder. 9 December 2004. Allgulander C, Florea I, Huusom AKT. Prevention of relapse in generalized anxiety disorder by escitalopram treatment. *International Journal of Neuropsychopharmacology* 2006;9(5):495-505[3]	
Indirect comparison of escitalopram versus benzodiazepines		
Diazepam vs placebo (DSM-IV diagnosed patients)		
Hackett et al[4].	Hackett, D., V. Haudiquet, and E. Salinas, A method for controlling for a high placebo response rate in a comparison of venlafaxine XR and diazepam in the short-term treatment of patients with generalised anxiety disorder. European Psychiatry, 2003. 18(4): 182-187.	
Supportive, non-randomised trial		

[4] In the Nov 06 submission it may have been inadvertantly identified as 99825.

Trial	Reports	Included in Nov 06 Submission
SCT-MD-17	An open-label extension study of the safety and efficacy of Lu-26-054 (i.e. escitalopram) in patients with generalised anxiety disorder. 31 October 2003. Davidson JRT, Bose A, Wang Q. Safety and efficacy of escitalopram in the long-term treatment of generalized anxiety disorder. *Journal of Clinical Psychiatry* 2005;66(11):1441-1446[5].	

B.2.3 Exclusion of trials

None of the randomised trials that met the inclusion criteria outlined above and in Attachment 4 were excluded.

Details of all the excluded studies have been presented in Tables 17, 18 and 19 in Attachment 4 and thus details of these studies are not re-presented. Table B.2.5 (adapted from Table 17, Attachment 4) and Table B.2.6 (adapted from Table 19, Attachment 4) summarise respectively the reasons for exclusion of trials that included escitalopram and benzodiazepines for generalised anxiety disorder.

Table B.2.5: Reasons to exclude each Escitalopram trial from further detailed assessment

Publication	Reason for Exclusion
Bielski, R.J., A. Bose, and C.C. Chang, A double-blind comparison of escitalopram and paroxetine in the long-term treatment of generalized anxiety disorder. Ann Clin Psychiatry, 2005. 17(2): p. 65-9.	No placebo arm
Goodman, W.K., A. Bose, and Q. Wang, Treatment of generalized anxiety disorder with escitalopram: pooled results from double-blind, placebo-controlled trials. J Affect Disord, 2005. 87(2-3): p. 161-7.	The trial population mentioned refers to Davidson et al, 2002, 2004 and data on file, 2002 which are all included in the submission.
Grant, J.E. and M.N. Potenza, Escitalopram treatment of pathological gambling with co-occurring anxiety: An open-label pilot study with double-blind discontinuation. International Clinical Psychopharmacology, 2006. 21(4): p. 203-209.	Not a randomized trial nor a relevant population
Ipser, J.C., P; Dhansay, Y; Fakier, N; Seedat, S; Stein, DJ, Pharmacotherapy augmentation strategies in treatment-resistant anxiety disorders. Cochrane Database of Systematic Reviews, 2007. 2.	Meta-analysis looking at augmentation in treatment resistant anxiety – not a relevant population
Mohamed, S., et al., Escitalopram for comorbid depression and anxiety in elderly patients: A 12-week, open-label, flexible-dose, pilot trial. Am J Geriatr Pharmacother, 2006. 4(3): p. 201-9.	Not a randomized trial; no comparator arm
National Institute of Mental Health (NIMH), Drug Therapy for Generalized Anxiety Disorder Among the Elderly. 2006, July, Clinical Trials.	Not a completed trial
New York State Psychiatric Institute. , F.L., Cognitive-Behavioral Therapy and Lexapro for GAD	Not a completed trial
Stein, D.J., H.F. Andersen, and W.K. Goodman, Escitalopram for the treatment of GAD: efficacy across different subgroups and outcomes. Ann Clin Psychiatry, 2005. 17(2): p. 71-5.	Subgroup analysis examined; original studies included in analysis -based on Goodman

Table B.2.6: Reasons to exclude each benzodiazepine trial from further detailed assessment

GAD Benzo HAM-A DSM-IV	Reason for Exclusion
Andreatini, R., et al., Effect of valepotriates (valerian extract) in generalized anxiety disorder: a randomized placebo-controlled pilot study. Phytother Res, 2002. 16(7): p. 650-4.	DSM-III- R
Ansseau, M., et al., Controlled comparison of the efficacy and safety of four doses of suriclone, diazepam, and placebo in generalized anxiety disorder. Psychopharmacology (Berl), 1991. 104(4): p. 439-43.	DSM-III-R
Borison, RL, Albrecht, JW, Diamond, BI. Efficacy and safety of a putative anxyiolitic agent: Ipsapirone. Psychopharmacology Bulletin. 1990;6(26):207-209	DSM-III
Boyer, WF, Feighner, JP. A placebo-controlled double-blind multicenter trial of two doses of ipsapirone versus diazepam in generalized anxiety disorder. International Clinical Psychopharmacology 1993;8:173-76	DSM-III
Casacalenda N et al. Pharmacologic treatments effective in both generalized anxiety disorder and major depressive disorder: clinical and theoretical implications. Canadian Journal of Psychiatry. 1998. 43(7): 722	DSM-III
Chessick, C.A., MH; Thase, ME; Batista Miralha da Cunha, ABC; Kapczinski, FFK; de Lima, MSML; dos Santos Souza, JJSS Azapirones for generalized anxiety disorder. Cochrane Database of Systematic Reviews, 2007. 2.	Review, DSM-III; used to identify individual trials
Coak, AL; Reilly, J; Morris, S. Thioridazine for anxiety and depressive disorders. Cochrane Database of Systematic Reviews. 2, 2007.	DSM-III
Cohn, J, Rickels, K. A pooled, double-blind comparison of the effects of buspirone, diazepam and placebo in women with chronic anxiety. Current Medical Research and Opinion 1989;11(5):304-20	M-A; DSM-III; relevant studies already included
Cooper, S.J., et al., Beta 2-adrenoceptor antagonism in anxiety. Eur Neuropsychopharmacol, 1990. 1(1): p. 75-7.	DSM-III
Downing, R.W. and K. Rickels, Early treatment response in anxious outpatients treated with diazepam. Acta Psychiatr Scand, 1985. 72(6): p. 522-8.	single arm study
Fontaine, R., et al., Bromazepam and diazepam in generalized anxiety: a placebo-controlled study with measurement of drug plasma concentrations. J Clin Psychopharmacol, 1983. 3(2): p. 80-7.	DSM III
Fontaine, R., G. Chouinard, and L. Annable, Bromazepam and diazepam in generalized anxiety: A placebo-controlled study of efficacy and withdrawal. Psychopharmacology Bulletin, 1984. 20(1): p. 126-127.	DSM III
Goldberg, H.L. and R. Finnerty, Comparison of buspirone in two separate studies. J Clin Psychiatry, 1982. 43(12 Pt 2): p. 87-91.	DSM III
Heideman J, van Rijswijk E, van Lin N, de Loos S, Laurant M, Wensing M, van de Lisdonk E, Grol R. Interventions to improve management of anxiety disorders in general practice: a systematic review. British Journal of General Practice. 2005;55(520):867-874	Review
Jacobson, A.F., et al., Comparison of buspirone and diazepam in generalized anxiety disorder. Pharmacotherapy, 1985. 5(5): p. 290-6.	no placebo; DSM-III
Jesinger, D.K. and N. Gostick, Anxiety neurosis in general practice. A double-blind comparative study of diazepam and clovoxamine, a novel inhibitor of noradrenaline and serotonin reuptake. Int Clin Psychopharmacol, 1989. 4(4): p. 301-11.	No placebo
Kapczinski, F.L., MS; Souza, JS; Cunha, A; Schmitt, R Antidepressants for generalized anxiety disorder. Cochrane Database of Systematic Reviews, 2007. 2.	M-A
King Pharmaceuticals Research and Development, A Study on the Effectiveness and Safety of Diazepam Injection (Vanquix™) for Patients With Epilepsy That Receive Antiepileptic Drugs, But Still Experience Acute Repetitive Seizures (Bouts or Clusters of Seizures) That Require Treatment. 2007.	trial not completed, inappropriate patient population
Llorca, P.M., et al., Efficacy and safety of hydroxyzine in the treatment of generalized anxiety disorder: A 3-month double-blind study. Journal of Clinical Psychiatry, 2002. 63(11): p. 1020-1027.	bromazepam
Mahe V. et al., Long-term pharmacological treatment of generalized anxiety disorder. International Clinical psychopharmacology. 2000;15(2):99-105	M-A; individual studies included in analysis
Martin JL., S.-P.M.F.T.M.-S.E.S.T.G.C., Review: Benzodiazepines in generalized anxiety disorder: heterogeneity of outcomes based on a systematic review and meta-analysis of clinical	MA - not published

GAD Benzo HAM-A DSM-IV	Reason for Exclusion
trials. Journal of Psychopharmacology, 2007. 21(7): p. 774-82.	
Meoni, P., D. Hackett, and M. Lader, Pooled analysis of venlafaxine XR efficacy on somatic and psychic symptoms of anxiety in patients with generalized anxiety disorder. Depression and Anxiety, 2004. 19(2): p. 127-132.	Re-analysis of 5 prior trials
Mitte K, Noack P, Steil R, Hautzinger M. A meta-analytic review of the efficacy of drug treatment in generalized anxiety disorder. Journal of Clinical Psychopharmacology. 2005;25(2):141-150	DSM-III
Miyasaka, L.A., AN; Soares, BGO Valerian for anxiety disorders. Cochrane Database of Systematic Reviews, 2007. 2.	Review; only Andreatini relevant and this is DSM-III-R
Murphy, S.M., R. Owen, and P. Tyrer, Comparative assessment of efficacy and withdrawal symptoms after 6 and 12 weeks' treatment with diazepam or buspirone. Br J Psychiatry, 1989. 154: p. 529-34.	diazepam, buspirone, no placebo
Pecknold, J.C., et al., Evaluation of buspirone as an antianxiety agent: buspirone and diazepam versus placebo. Can J Psychiatry, 1989. 34(8): p. 766-71.	DSM-III
Pecknold, JC, Familamiri, P, Chang, H, Wilson, R, Alarcia, J, Mc-Clure, J. Buspirone: Anxiolytic?. Progress in Neuro-psychopharmacol-ogy & Biological Psychiatry 1985;9:638-642	DSM-III
Pomara, N., et al., Cortisol response to diazepam: its relationship to age, dose, duration of treatment, and presence of generalized anxiety disorder. Psychopharmacology (Berl), 2005. 178(1): p. 1-8.	measurement of cortisol
Pourmotabbed, T., et al., Treatment, discontinuation, and psychomotor effects of diazepam in women with generalized anxiety disorder. J Clin Psychopharmacol, 1996. 16(3): p. 202-7.	DSM-III -R
Power KG et al, "A controlled comparison of cognitive-behaviour therapy, diazepam, and placebo, alone and in combination, the treatment for generalized anxiety disorder. J. anxiety disorder. 1990. 4(4):267-292	DSM-III
Rickels, K., et al., Antidepressants for the treatment of generalized anxiety disorder. A placebo-controlled comparison of imipramine, trazodone, and diazepam. Arch Gen Psychiatry, 1993. 50(11): p. 884-95.	DSM-III
Rickels, K., et al., Buspirone and diazepam in anxiety: a controlled study. J Clin Psychiatry, 1982. 43(12 Pt 2): p. 81-6.	DSM-III
Rickels, K., et al., Gepirone and diazepam in generalized anxiety disorder: a placebo-controlled trial. J Clin Psychopharmacol, 1997. 17(4): p. 272-7.	DSM-III
Rickels, K., N. DeMartinis, and B. Aufdembrinke, A double-blind, placebo-controlled trial of abecarnil and diazepam in the treatment of patients with generalized anxiety disorder. J Clin Psychopharmacol, 2000. 20(1): p. 12-8.	DSM-III -R
Rocca, P., et al., Paroxetine efficacy in the treatment of generalized anxiety disorder. Acta Psychiatr Scand, 1997. 95(5): p. 444-50.	no placebo
Ross, CA,Matas, M. A Clinical Trial of Buspirone and Diazepam in the Treatment of Generalized Anxiety Disorder. Canadian Journal of Psychiatry 1987;32:351-355	buspirone and diazepam, no placebo
Rynn, M., et al., Early response and 8-week treatment outcome in GAD. Depression and Anxiety, 2006. 23(8): p. 461-465.	DSM-III
Shah, L.P., et al., A controlled double blind clinical trial of buspirone and diazepam in generalised anxiety disorder. Indian Journal of Psychiatry. Vol, 1990. 32(2): p. 166-169.	no placebo DSM-III
Strand, M., et al., A double-blind, controlled trial in primary care patients with generalized anxiety: a comparison between buspirone and oxazepam. J Clin Psychiatry, 1990. 51 Suppl: p. 40-5.	buspirone and oxazepam
Tyrer, P. and R. Owen, Anxiety in primary care: is short-term drug treatment appropriate? J Psychiatr Res, 1984. 18(1): p. 73-8.	DSM-III, crossover trial
Tyrer, P., et al., The Nottingham study of neurotic disorder. Effect of personality status on response to drug treatment, cognitive therapy and self-help over two years. Br J Psychiatry, 1993. 162: p. 219-26.	DSM-III
Tyrer, P., et al., The Nottingham study of neurotic disorder: comparison of drug and psychological treatments. Lancet, 1988. 332(8605): p. 235-40.	DSM-III
University of Utah, P.C.s.M.C.F., Intranasal Midazolam Versus Rectal Diazepam for Treatment of Seizures. 2006.	trial not completed, inappropriate patient population
Wingerson, D.K., et al., Effect of benzodiazepines on plasma levels of homovanillic acid in anxious patients and control subjects. Psychiatry Res, 1996. 65(1): p. 53-9.	intravenous diazepam, plasma HVA levels

B.2.4 Key aspects of identified trials

Table B.2.7 summarises the key design and population characteristics of the nine identified trials - seven direct comparative studies of escitalopram versus placebo, one utilised in the indirect comparison (placebo versus diazepam), and one supportive study (open-label continuation of escitalopram). The main primary and secondary outcomes for the studies are also presented.

Table B.2.7: Comparative summary of characteristics of comparative randomised trials

Trial ID	Design characteristics [a]	Compared interventions (*N*, drug, dose, frequency, duration)	Summary of main population characteristics	Main outcomes	
				Primary	Secondary
Escitalopram Studies					
SCT-MD-05 Patients completing this study were eligible to enter a 24-week open label extension (SCT-MD-17)	RCT, DB, PG, flexible dose	placebo escitalopram: 10-20mg/day 8 weeks	N=254 DSM-IV criteria for GAD Age: 18-80	Efficacy Change from baseline to wk8 in HAM-A total score using LOCF Safety AEs, laboratory values, physical examination, ECG and vital signs	HAM-A psychic anxiety subscale CGI-I CGI-S
SCT-MD-06 Patients completing this study were eligible to enter a 24-week open label extension (SCT-MD-17)	RCT, DB, PG, flexible dose	placebo escitalopram: 10, 20mg/day 8 weeks	N=287 DSM-IV criteria for GAD Age: 18-73	Efficacy HAM-A Safety AEs, laboratory values, physical examination, ECGs, vital signs	HAM-A psychic anxiety subscale CGI-I CGI-S
SCT-MD-07 Patients completing this study were eligible to enter a 24-week open label extension (SCT-MD-17) Davidson, J.R.T., et al., 2004	RCT, DB, PG, flexible dose	placebo escitalopram: 10, 20mg/day 8 weeks	N=315 DSM-IV criteria for GAD Age: 18-80	Efficacy HAM-A Safety AEs, laboratory values, physical examination, ECGs, vital signs	HAM-A psychic anxiety subscale CGI-I CGI-S
SCT-MD-17 Patients from studies: SCT-MD-05, SCT-MD-06, SCT-MD-07 Davidson, J.R.T et al., 2005	OL, flexible dose	Escitalopram: 10-20mg/day 24 weeks	N=526 DSM-IV criteria for GAD Age: 18-79	Efficacy HAM-A HAM-A psychic anxiety subscale CGI-I CGI-S HAD HAM-D	Safety AEs, laboratory values, physical examination, ECGs, vital signs QOL Quality of life scale
SCT-MD-31	MC, DB, PG, RCT, flexible	Escitalopram: 10-20mg/day	N=392 Age: 18-65	HAM-A	HAMA Psychic Anxiety Subscale

Trial ID	Design characteristics [a]	Compared interventions (*N*, drug, dose, frequency, duration)	Summary of main population characteristics	Main outcomes	
				Primary	Secondary
	dose	Venlafaxine XR: 75-225 mg/day Placebo 8 weeks	DSM-IV criteria for GAD		CGI-S CGI-I Adverse events and vital signs

Trial ID	Design characteristics [a]	Compared interventions (*N*, drug, dose, frequency, duration)	Summary of main population characteristics	Main outcomes	
				Primary	Secondary
99815 Baldwin D.S., et al. 2006	RCT, DB, MN, MC, PG, FD	placebo escitalopram: 5, 10, 20mg/day paroxetine: 20mg/day 12 weeks	N=650 DSM-IV –TR criteria for a primary diagnosis of GAD HAM-A≥20 HAM-A items 1 (anxious mood) and 2 (tensions) ≥2 Age: 18-65	Efficacy Change from baseline to wk12 in HAM-A total score using LOCF Safety AEs, DESS checklist(for patients completing the study), clinical safety laboratory tests, ECGs, vital signs, weight/BMI	HAM--A HAM-A psychic anxiety subscale score HAM-A somatic anxiety subscale score HAM-A score for item 1 (anxious mood) HAM-A score for item 2 (tension) HAD anxiety score CGI-S CGI-I SDS Proportion of responders (≥reduction in HAM-A) Proportion of remitters (patients with a HAM-A total score ≤ 9) Proportion of responders (CGI-I score ≤ 2) Exploratory efficacy endpoint -Proportion of remitters (patients with HAM-A total score ≤ 27) Assessment of depression HAD depression score

Trial ID	Design characteristics [a]	Compared interventions (*N*, drug, dose, frequency, duration)	Summary of main population characteristics	Main outcomes	
				Primary	Secondary
99769 Allgulander, et al, 2006	RCT, DB, MC	placebo escitalopram: 20mg/day open label: 12 weeks DB: 26-78 weeks	open label: N=491 DB: N=375 DSM-IV –TR criteria for a primary diagnosis of GAD HAM-A≥20 at screening and at baseline HAM-A items 1 (anxious mood) and 2 (tensions) ≥2 at screening and at baseline MADRS total score ≤16 at screening and at baseline Age: 18-65	Efficacy Time to relapse of GAD in the double-blind period (relapse was defined as either an increase in HAM-A-A total score 15 ≥ or lack of efficacy as judged by the investigator Safety AEs, clinical safety laboratory tests, vital signs, weight and physical examination	HAM-A total score HAM-A psychic anxiety subscale HAM-A somatic anxiety subscale HAM-A score for item 1 (anxious mood) HAM-A score for item 2 (tension) HAD anxiety subscale CGI-S score per visit CGI-S score CGI-I score SDS (work, family, life, social life) scores
Benzodiazepine Study (diazepam)					
Hackett, D., V. Haudiquet, and E. Salinas, A method for controlling for a high placebo response rate in a comparison of venlafaxine XR and diazepam in the short-term treatment of patients with generalised anxiety disorder. European Psychiatry, 2003. 18(4): p. 182-187.	MC, DB, PG, RCT	Diazepam: 15mg/day Venlafaxine XR: 75 or 150 mg/day Placebo 8 weeks	N=540 Age:> 18 DSM-IV criteria for GAD	HAM-A HAMA Psychic Anxiety Subscale HAD HAD anxiety sub-scale CGI-I	Adverse events and vital signs

AE = adverse events; C-O = cross-over; DB = double-blind; DBP = diastolic blood pressure; ITT = intention to treat; MC = multicentre; MN = multinational; PG = parallel group; PP = per protocol analysis; RCT = randomised controlled trial; LOCF= last observation carried forward; DESS = Discontinuation Emergent Signs and Symptoms; AEs =adverse events; electrocardiograms = ECG

B.3 Assessment of the measures taken by investigators to minimise bias in the direct randomised trials

Summary

An assessment of the measures taken by investigators to minimise bias in the direct, randomised, controlled studies comparing escitalopram with placebo (comparator one) is presented (Studies SCT-MD-05, SCT-MD-06, SCT-MD-07, 99769, 99815). An indirect comparison of escitalopram with benzodiazepines (comparator 2) is also presented– using placebo as a common comparator The comparison is made using the direct, randomised controlled studies comparing escitalopram with placebo and a published study (Hackett et al.[4]) comparing placebo with benzodiazepine (diazepam) in DSM-IV diagnosed GAD patients.

An assessment of the measures taken by investigators to minimise bias in the escitalopram versus placebo studies and the placebo versus diazepam study (Hackett et al.[4]) has been presented in Sections B.3.1-B.3.4. The studies comparing escitalopram and placebo are randomised, controlled, double-blind trials. There is sufficient information provided in the Clinical Study Reports on the methods of randomisation and blinding and adequacy of follow-up to conclude that the trials were well designed to minimise bias.

The escitalopram versus placebo studies were randomised by a third party (sponsor pharmaceutical company) ensuring patients were validly randomised to the treatment group. The study products were indistinguishable from one another since they were identical in appearance, shape, taste and smell. The supply of identical study products ensured that patients, investigators and outcomes assessors were blinded to study treatment allocation. All efficacy analyses were conducted on the ITT population, defined as all randomised patients receiving at least one dose of study medication and having one valid post baseline assessment of the (continuous) primary efficacy variable. The efficacy analyses were performed using the Last Observation Carried Forward (LOCF) approach.

The study comparing placebo and benzodiazepines(Hackett et al.[4]) was also stated to be a randomised, controlled, double-blind study but there was insufficient detail provided on the methods of randomisation, blinding and adequacy of patient follow-up in the publication to assess the minimisation, or otherwise, of bias in the trial.

Information on the assessment of bias in a supportive long-term open-label extension study is also provided.

All the information provided in Section B.3 was sourced from the Clinical Study Reports for Studies SCT-MD-05, SCT-MD-06, SCT-MD-07, SCT-MD-31, 99815 and 99769. These reports are provided in hard copies of in a clearly labelled folder. The publication by the publication by Hackett et al[4] was the only source of information on this study, as it is not a sponsor-conducted study and therefore no Clinical Study Report is available. This published reference is in the folder of references provided.

Information is provided on the studies comparing escitalopram with placebo (comparator one) first, followed by information on the study comparing placebo and benzodiazepine (diazepam) in DSM-IV diagnosed patients (utilised in the indirect comparison of escitalopram and benzodiazepines, along with the escitalopram versus placebo studies).

A summary of randomisation, blinding, the basis of the analyses and adequacy of follow-up for each of the randomised controlled trials is presented in Section B.3.1-B.3.4. A more detailed assessment of the measures taken to minimise bias in each of the randomised controlled trials is presented in Attachment 5.

A summary of the information available to assess the measures taken by the investigators to minimise bias in the studies used for the indirect comparison of escitalopram and benzodiazepines (comparator 2) is presented in Section B.3.5.

Information on the non-randomised, open-label extension study is provided separately in Section B.3.6.

B.3.1 Randomisation

Escitalopram versus placebo studies

The studies comparing escitalopram and placebo were randomised, controlled, double-blind, placebo-controlled, parallel group trials. Eligible patients were randomised to double-blind treatment with either escitalopram or placebo according to a randomisation code generated by the sponsor. At each centre the randomisation code was to be applied consecutively.

Placebo versus benzodiazepine study

It is stated in the publication that the study by Hackett et al.[4] was a multicentre, randomised, double-blind, placebo-controlled, parallel-group study. No details of the randomisation method are provided.

B.3.2 Blinding

Escitalopram versus placebo studies

For the double-blind treatment period patients were provided with identically appearing study product (tablets in Study SCT-MD-05, SCT-MD-06, SCT-MD-07, SCT-MD-31, 99769; capsules in Study 99815). The study products were indistinguishable from one another since they were identical in appearance, shape, taste and smell. Thus all participants, investigators and outcomes assessor could not be aware of the treatment the patient was randomised to. The randomisation code could only be unbroken in an emergency and this did not occur with any patient in any of the studies.

Placebo versus benzodiazepine study

It is stated in the publication that the study by Hackett et al.[4] was a multicentre, randomised, double-blind, placebo-controlled, parallel-group study. No details of blinding are provided.

B.3.3 Basis of the analyses

Escitalopram versus placebo studies

The following analysis sets were defined *a priori* in all the studies:

Randomised population - all patients randomised into the study

Safety Population – all randomised patients who took at least one dose of double-blind study medication

Intent-to-Treat (ITT) population consisted of all patients in the safety population with at least one post-baseline efficacy assessment of the primary efficacy variable.

All efficacy analyses were conducted on the ITT population. The analyses were performed using the Last Observation Carried Forward (LOCF) approach. All safety analyses were conducted on the Safety Population.

In Study 99815 and 99769 the ITT population was called the "Full-analysis set (FAS)". Additional per protocol populations were defined in Study 99815 and Study 99769, however details and results of these populations are not presented in the Submission as they are not relevant.

Placebo versus benzodiazepine study

Hackett et al.[4] reported that randomised patients who had received at least one dose of study medication and who had at least one evaluation on one of the primary efficacy parameters, either during therapy, or within 3 days of the last treatment, constituted the intent-to-treat population (ITT) for the evaluation of efficacy. The safety population was evaluated in the randomised population. The primary efficacy analysis was carried out using the LOCF method to impute missing data.

A summary of the measures undertaken to minimise bias in the key randomised, controlled trials is presented in Table B.3.1.

Table B.3.1: Summary of the measures undertaken to minimise bias in the randomised, controlled trials

Trial ID	Concealment of randomisation[a]	Blinding			Basis of analysis[b]
		Participants	Investigators	Outcomes assessors	
Escitalopram versus placebo					
SCT-MD-05	B (p .29, 30)	Yes (p. 30)	Yes (p. 30)	Yes (p. 30)	E[c, d] (p. 42)
SCT-MD-06	B (p. 27, 29)	Yes (p. 29)	Yes (p. 29)	Yes (p. 29)	E[c, d] (p. 41)
SCT-MD-07	B (p. 27, 29)	Yes (p. 29)	Yes (p. 29)	Yes (p. 29)	E[c, d] (p. 41)
SCT-MD-31[5]					
99815	B (p. 28, 29)	Yes (p. 27-29)	Yes (p. 27-29)	Yes (p. 27-29)	E[d, e] (p. 39)
99769	B (p. 28, 29)	Yes (p. 29)	Yes (p. 29)	Yes (p. 29)	Yes (p. 29)
BZD versus placebo					
Hackett et al.	NR[f]	NR[f]	NR[f]	NR[f]	E[g] (p. 183)

a A = central telephone randomisation service; B = third-party randomisation service (eg pharmacy, pharmaceutical company);
C = sequentially labelled, fully opaque, sealed envelopes
b D = intention-to-treat (all randomised participants: specify how the analysis dealt with missing data); E = all treated
participants (specify how the analysis dealt with missing data); F = per protocol participants; G = other (specified)
c The ITT population consisted of all randomised patients who received at least one dose of double-blind study medication with at least one post-baseline efficacy assessment on the HAM-A.
d. Last Observation Carried Forward (LOCF) was used in the analysis to account for missing data (SCT-MD-05 p. 44, SCT-MD-06 p. 42, SCT-MD-07 p. 42, 99815 p. 42)

[5] This was not available at the time of the submission.

e. All efficacy analyses were conducted on the full-analysis-set (FAS), i.e. all randomised patients who took at least one dose of study medication and who had at least one valid post-baseline assessment of the primary efficacy variable. Safety analyses (except analyses of DESS) were based on the all-patients-treated set (APTS), i.e. all randomised patients who took at least one dose of study medication. DESS analyses were conducted on the all-patients-completed set (APCS), i.e. all patients in the FAS who completed 12 weeks of double-blind treatment
f. The study is reported as being double-blind and randomised. No details of blinding or randomisation are given.
g. The analysis population was "randomised patients who had received at least one dose of study medication and who had at least one evaluation on one of the primary efficacy parameters, either during therapy, or within 3 days of the last treatment".
BZD = benzodiazepine, DESS = Discontinuation Emergent Signs and Symptoms, HAM-A = Hamilton Anxiety Scale
All page number references refer to the relevant Study Report, or for Hackett et al. the publication.

B.3.4 Adequacy of follow-up

Escitalopram versus placebo studies

The flow of participants through the individual randomised, controlled trials comparing escitalopram with placebo was well documented in the Study Reports. Data from the majority of patients randomised into the studies was analysed in the efficacy analyses (over 95%).

Placebo versus benzodiazepines study

The flow of participants in each treatment arm of the study by Hackett et al. was poorly documented, with only the number of patients discontinued and the number of patients analysed reported.

Table B.3.2 summarises the flow of participants in the key randomised, controlled trials.

Table B.3.2: Flow of participants through the key randomised, controlled trials

Trial ID • Intervention arm	No. randomised	Did not receive intervention	Lost to follow-up	Dis-continued	Analysed
Escitalopram vs placebo					
SCT-MD-05					
• Escitalopram	129	3 (2.3%)	4 (3.1%)	29[a] (23%)	124[b] (96%)
• Placebo	128	0 (0%)	8 (6.3%)	33[a] (26%)	128 (100%)
SCT-MD-06					
• Escitalopram	149	4 (2.7%)	7 (4.7%)	27[a] (18%)	143[c] (96%)
• Placebo	145	3 (2.1%)	10 (6.9%)	28[a] (19.%)	138[d] (95%)
SCT-MD-07					
• Escitalopram	161	3 (1.9%)	12 (7.5%)	39[a] (24%)	154[d] (96%)
• Placebo	159	2 (1.3 %)	12 (7.5%)	34[a] (21.%)	153[e] (96%)
SCT-MD-31[f]					
• Escitalopram	131	4 (3.0%)	4 (3.0%)	29 (22%)	125 (95%)
• Placebo	140	4 (2.9 %)	4 (2.9%)	36 (26%)	135 (96%)
99815					
• Escitalopram 10mg	136	0 (0%)	2 (1.5)	18 (13%)	134 (99%)
• Escitalopram 20mg	133	0 (0%)	0 (0)	22 (17%)	132 (99%)
• Placebo	139	0 (0%)	0 (0)	15 (11%)	138 (99%)
99769					
• Escitalopram	187	1[g] (0.5%)	8 (4.3%)	71 (38%)	186 (99%)
• Placebo	188	1[g] (0.5 %)	4 (2.1%)	136 (72%)	187 (99%)
BZD vs placebo					
Hackett et al.					
• Diazepam 15mg d	NR[h]	NR[h]	NR	14[i]	89
• Placebo	NR[h]	NR[h]	NR	16[i]	97

a. This figure does not include the patients who "Did not receive intervention".
b. 2 patients had no post-baseline primary efficacy (HAM-A) assessment and therefore were not included in the ITT efficacy population (as defined in the trial), in addition to the 3 patients who did not receive the intervention
c. 2 patients had no post-baseline primary efficacy (HAM-A) assessment and therefore were not included in the ITT efficacy population (as defined in the trial), in addition to the 4 patients who did not receive the intervention
d. 4 patients had no post-baseline primary efficacy (HAM-A) assessment and therefore were not included in the ITT efficacy population (as defined in the trial), in addition to the 3 patients who did not receive the intervention
e. 4 patients had no post-baseline primary efficacy (HAM-A) assessment and therefore were not included in the ITT efficacy population (as defined in the trial), in addition to the 2 patients who did not receive the intervention
f. Details of the venlafaxine XR treatment arm not detailed, as it is not a comparator
g. 1 patient was randomised into each treatment group even though they were not eligible for randomisation
h. The study consisted of 4 treatment arms – diazepam, placebo and two different doses of venlafaxine XR. Only the diazepam and placebo results are reported in the submission. In total 564 patients entered the study, 556 received at least one dose of study medication and were included in the randomised population. 16 patients failed to provide a primary efficacy evaluation on therapy. The remaining 540 patients constituted the defined ITT population. The patient numbers in the individual treatment arms are not provided.

i. Patients discontinued in the analysed population only are reported.

B.3.5 Assessment of the measures taken to minimise bias in the indirect comparison of escitalopram and benzodiazepines

In order to compare escitalopram with benzodiazepines (comparator 2) an indirect comparison using the escitalopram versus placebo studies and placebo versus benzodiazepine study is undertaken in this submission. Note that studies utilised in this indirect comparison that compare escitalopram with placebo also provide a direct comparison of escitalopram with comparator 1 (placebo).

An assessment of the measures taken by investigators to minimise bias in the escitalopram versus placebo studies and the placebo versus diazepam study (Hackett et al.[4]) has been presented in Sections B.3.1-B.3.4. The studies comparing escitalopram and placebo are randomised, controlled, double-blind trials. There is sufficient information provided in the Clinical Study Reports on the methods of randomisation and blinding and adequacy of follow-up to conclude that the trials were well designed to minimise bias.

Hackett et al.[4] was also stated to be a randomised, controlled, double-blind study but there was insufficient detail provided on the methods of randomisation, blinding and adequacy of patient follow-up in the publication to be able to assess the adequacy of the measures taken by investigators to minimise bias in the trial.

B.3.6 Assessment of the measures taken to minimise bias in the non-randomised, open-label extension study

Supportive study SCT-MD-17 is a 24-week open, label extension of key Studies SCT-MD-05, SCT-MD-06 and SCT-MD-07. The objective of the study was to evaluate the safety and efficacy of long-term escitalopram treatment of GAD.

All patients who completed these randomised, controlled studies were then invited to participate in an open-label extension Study. Thus there was no randomisation or blinding in the study.

A total of 526 patients were enrolled in the extension study and received at least one dose of escitalopram and were included in the Safety Population. A total of 521 patients also received at least one dose of study medication and had at least one post baseline assessment of the primary efficacy variable and thus were included in the ITT population. Patient disposition in the study is presented in Table B.3.3.

Table B.3.3: Patient disposition in the supportive open-label extension study (SCT-MD-17)

	Escitalopram (N=526) n (%)*
Completers	299 (56.8)
Withdrawn for any reason	227 (43.2)
Lost to Follow-up	65 (12.4)

Source: Panel 7, p. 45 of Study Report
* % figures based on Safety Population

Source Documents

Data is extracted from the relevant Study Reports and the published paper Hackett et al[4]. Full page and table references are provided in Attachment 5.

B.4 Characteristics of the direct randomised trials

Section B.4 contains details of the characteristics of the seven key randomised, controlled studies (Study 99270, 99012 and 99269) comparing escitalopram with placebo (comparator 1). An indirect comparison between escitalopram and benzodiazepines (comparator 2) is also provided, using placebo as a common comparator. One study (Hackett et al.) compares placebo and diazepam in DSM-IV diagnosed patients with GAD, which is then compared with the escitalopram versus placebo studies. All patients included in the studies have moderate to severe GAD. Patients did not have other psychiatric co-morbidities.

The treatment studies were all parallel group, randomised controlled trials of 8 weeks (Study SCT-MD-05, SCT-MD-06, SCT-MD-07, SCT-MD-31) or 12 weeks (Study 99815) duration. Study 99769 was a relapse prevention study with patients receiving 12 weeks of open-label escitalopram, with responders then randomised to receive a further 24 weeks therapy with either flexible-dose escitalopram or placebo. Patients were randomised to either a fixed dose of escitalopram or placebo (Study 99815), or a flexible dose of escitalopram (Study SCT-MD-05, SCT-MD-06, SCT-MD-07, SCT-MD-31). Full details of the interventions received are presented in Section B.4.2, including details of the actual escitalopram doses taken. In addition, details of a supportive non-randomised, open-label extension follow-on study (Study SCT-MD-17) are also provided.

The baseline characteristics of patients (age, sex, race, duration and onset of GAD) across the studies and in the treatment arms within studies were all similar, except for the relapse prevention study. Further details are provided in Section B.4.4.

The characteristics of patients included in the key randomised, controlled trials are presented in Section B.4.1 to Section B.4.3. The eligibility criteria are detailed followed by the baseline demographic and clinical characteristics of the patients. The study designs are explained, including the daily dose of the interventions received in each treatment group in each study (escitalopram versus placebo and placebo versus benzodiazepine) and the duration of the trials. All trials have been completed.

A summary of the characteristics of the randomised trials utilised in the indirect comparison of escitalopram and benzodiazepines (comparator 2) is presented in Section B.4.4.

The characteristics of the supportive, non-randomised, open-label extension study are presented in Section B.4.5.

Full details of each study is available in the Study Report provided, with clear cross-referencing in this submission to the relevant pages and tables. The publication by Hackett et al.[4] is provided in the folder of References.

A summary of the trial characteristics for the key studies included in this submission (escitalopram vs placebo: Studies SCT-MD-05, SCT-MD-06, SCT-MD-07, SCT-MD-31, 99815 and 99769; placebo vs benzodiazepines: Hackett et al.[4]) is provided in Table B.4.1.

Table B.4.1: Summary of the characteristics of the included trials (Study SCT-MD-05, SCT-MD-06, SCT-MD-07, SCT-MD-31, 99815, 99789, Hackett et al., SCT-MD-17)

Trial ID	Design / Duration	Size*	Location	Dosage regimen	Trial population
SCT-MD-05	Randomised, double-blind, placebo-controlled, parallel group, flexible dose study of ESC versus placebo - 1 week run-in - 8 week randomised phase	252 patients ESC 124 Placebo 128	25 centres in the United States	ESC once daily – initially 10mg once daily, increased to 20mg daily if required after Week 4. - Placebo once daily	Adult GAD patients (DSM-IV criteria) Moderate to severe disability (based on HAM-A score ≥18) No co-morbidities
SCT-MD-06	Randomised, double-blind, placebo-controlled, parallel group, flexible dose study of ESC versus placebo - 1 week run-in - 8 week randomised phase	287 patients ESC 145 Placebo 142	19 centres in the United States	ESC once daily – initially 10mg once daily, increased to 20mg daily if required after Week 4. - Placebo once daily	Adult GAD patients (DSM-IV criteria) Moderate to severe disability (based on HAM-A score ≥18) No co-morbidities
SCT-MD-07	Randomised, double-blind, placebo-controlled, parallel group, flexible dose study of ESC versus placebo - 1 week run-in - 8 week randomised phase	307 patients ESC 154 Placebo 153	25 centres in the United States	ESC once daily – initially 10mg once daily, increased to 20mg daily if required after Week 4. - Placebo once daily	Adult GAD patients (DSM-IV criteria) Moderate to severe disability (based on HAM-A score ≥18) No co-morbidities
SCT-MD-31	Randomised, double-blind, placebo-controlled, parallel group, flexible dose study of ESC versus placebo versus venlafaxine - 1 week run-in - 8 week randomised phase	385 patients ESC 125 Placebo 135 Venlafaxine 125	28 centres in the United States	Relevant study arms: - ESC once daily – initially 10mg once daily, increased to 20mg daily if required after Week 1. - Placebo once daily Other study arm: - venlafaxine XR 75-225mg once daily	Adult GAD patients (DSM-IV criteria) Moderate to severe disability (based on HAM-A score ≥20) No co-morbidities

Trial ID	Design / Duration	Size*	Location	Dosage regimen	Trial population
99815	Randomised, double-blind, placebo-controlled, parallel group, fixed dose study of various doses of ESC versus placebo - 1 week run-in - 12 week randomised phase - 2 week washout period	681 patients ESC 5mg 134 ESC 10mg 134 ESC 20mg 132 Paroxetine 20mg 136 Placebo 138	63 centres in 10 European countries, including the UK	Relevant study arms: - ESC 10mg once daily – ESC 20mg once daily - Placebo once daily Other study arms: - ESC 5mg once daily - paroxetine 20mg once daily	Adult GAD patients (DSM-IV-TR criteria) Moderate to severe disability (based on HAM-A score ≥20) No co-morbidities
99769	Randomised, double-blind, placebo-controlled, parallel group, fixed dose study of ESC versus placebo in relapse prevention - 12 open-label run-in with ESC - 24 week randomised phase - 2 week double-blind down-tapering period	373 patients ESC 186 Placebo 187	59 centres in 7 European countries and Canada	Relevant study arms: - ESC 20mg once daily - Placebo once daily	Adult GAD patients (DSM-IV-TR criteria) Moderate to severe disability (based on HAM-A score ≥20) No co-morbidities
Hackett et al.	Randomised, double-blind, placebo-controlled, parallel group, fixed dose study of placebo, diazepam and 2 doses of venlafaxine - 8 week randomised phase - no other study design details provided	556 patients Placebo 97 Diazepam 15mg 89 Venlafaxine 75mg 191 Venlafaxine 150mg 179	Not reported	Relevant study arms: - Placebo once daily – Diazepam 15mg once daily Other study arms: - Venlafaxine XR 75mg once daily - Venlafaxine XR 150mg once daily	Adult GAD patients (DSM-IV criteria) Moderate to severe disability (based on HAM-A score ≥20) No co-morbidities

Trial ID	Design / Duration	Size*	Location	Dosage regimen	Trial population
SCT-MD-17	Open-label, flexible dose extension study in patients previously receiving ESC or placebo in Studies SCT-MD-05, SCT-MD-06 and SCT-MD-07 - 24 week study	521 patients	63 centres in the United States	ESC 10-20mg once daily	Adult GAD patients (DSM-IV criteria) Must have completed Study SCT-MD-05, SCT-MD-06 or SCT-MD-07

ESC = escitalopram

- ITT population size reported

B.4.1 Selection of the study population

The key studies included adult patients with GAD diagnosed based on DSM-IV criteria.

For inclusion, patients had to have a Hamilton Anxiety Scale (HAM-A) score of ≥18 (SCT-MD-05, SCT-MD-06, SCT-MD-07 or ≥20 (SCT-MD-31, 99815, 99769, Hackett et al.[4]) at baseline. The HAM-A is considered the gold standard scale for measuring the severity of illness in patients with GAD[6]. A HAM-A score of <17 is considered mild, a score of 18-24 mild-moderate, while 25-30 is considered to indicate moderate to severe anxiety (reference www.cnsforum.com) Thus patients recruited into the studies had moderate to severe GAD.

A further inclusion criteria based on HAM-A was the requirement to have a score of ≥2 on both the HAM-A item 1 (anxious mood) and item 2 (tension) at screening and baseline. This is because the HAM-A is not specific to GAD, but designed to measure anxiety more broadly. Anxious mood and psychic tension concentrate on specific factors particularly relevant to DSM-IV GAD and have been used together as a pivotal subscale in other placebo-controlled studies[6].

Patients also had to have a low score on a depression rating scale at screening/baseline visits to be included in the studies, namely a:
HAMD[6] Total Score ≤17 in SCT-MD-05/-06/-07/-31, or
MADRS[7] Total Score of ≤16 (in 99769, 99815), or
Covi Anxiety Scale score which was greater than his/her RDS[8] score (in SCT-MD-05/-06/-07, Hackett et al.) and a total RDS score ≤9 (in Hackett et al.).

Other comorbid psychiatric conditions were also listed in the exclusion criteria in all studies. GAD is associated with high levels of lifetime comorbidity with other psychiatric disorders, including depression. However a sizeable proportion of patients with GAD suffer from GAD alone and GAD is recognised in DSM-IV as a distinct entity. It is important to demonstrate that the effect of the agent on GAD is specific and not due to secondary therapeutic effects on other comorbid conditions, such as depression. It is therefore recommended that comorbid conditions need to be controlled in pivotal efficacy studies[6].

The eligibility criteria for the key randomised, controlled studies are presented in Table B.4.2.

[6] Hamilton Depression Rating Scale

[7] Montgomery and Åsberg Depression Rating Scale

[8] Raskin Depression Scale

Table B.4.2: Eligibility criteria in the randomised, controlled trials

Trial ID	Inclusion criteria	Exclusion criteria
Escitalopram versus placebo		
SCT-MD-05 SCT-MD-06 SCT-MD-07	Male or female outpatient between 18-80 years Meet DSM-IV criteria for GAD Written informed consent Had a score of 18 or higher on the HAM-A with a minimum score of 2 on the tension and anxiety items at screening and baseline. Had a Hamilton Depression Rating Score of 17 or lower at the screening and baseline visits. Had a Covi Anxiety Scale score which was greater than his/her Raskin Depression Scale score at the screening and baseline visits. Had a normal physical examination, laboratory test and ECG results from the screening visit or clinically insignificant abnormalities.	Pregnant or breastfeeding women or women of childbearing potential not practising a reliable method of birth control. Met DSM-IV criteria for: Bipolar Disorder; Schizophrenia or any Psychotic Disorder; Obsessive Compulsive Disorder; Mental Retardation or any Pervasive Development Disorder or Cognitive Disorder. Principal diagnosis meeting DSM-IV criteria for any Axis I disorder other than GAD Personality Disorder of sufficient severity to interfere with their participation in the study History of any Psychotic Disorder, as defined by DSM-IV Any psychotic features At suicide risk, or who had made a serious suicide attempt within one year prior to the start of the study Met DSM-IV criteria for Substance Abuse or Dependence (other than nicotine) within six months prior to the study start Any malignancy (other than excised basal cell carcinoma) or any clinically significant haematological, endocrine, cardiovascular, renal, hepatic, gastrointestinal or neurological disease. Patients with such histories who had been stable for at least one year prior to the start of the study and judged by the investigator not to interfere with the patient's participation in the study. Systolic blood pressure greater than 180 mm Hg or less than 90 mm Hg or diastolic blood pressure greater than 105 mm Hg or less than 50 mm Hg at the screening or baseline visits. Treated with a depot neuroleptic within 6 months prior to study entry Treated with any neuroleptic, antidepressant or anxiolytic medication within 2 weeks (5 weeks for fluoxetine) prior to the first administration of double-blind study medication. Had received regular daily therapy with any benzodiazepine within one month prior to the first administration of double-blind study medication. Required concomitant treatment with any psychotropic drug (except zolpidem for sleep) or any drug with a psychotropic component Required concomitant therapy with any prohibited prescription or over-the-counter medication Had been in an investigational study within 1 month prior to study entry or who had received treatment with an investigational drug within 1 month or 5 half-lives, whichever was longer. Had participated in an investigational drug study for the treatment of depression within one year prior to study entry Had been in a previous investigational study of escitalopram Allergy or hypersensitivity to citalopram Had previously failed to respond to an adequate trial of citalopram or to adequate trials of two other SSRIs. Required ECT or had received ECT within 3 months prior to study entry Would require behaviour therapy or psychotherapy during the study Tested positive for alcohol, illicit drugs, or any prohibited medication on the urine drug screen Employees or relative of employees of the investigational site Unable to speak, read and understand English or who were judged by the investigator to be unable or unlikely to follow the study protocol.

Trial ID	Inclusion criteria	Exclusion criteria
		Not suitable for the study (in the opinion of the investigator)
SCT-MD-31[9]	Males and female outpatients between 18-65 years of age at baseline Had a primary diagnosis of GAD according to the DSM-IV criteria Written informed consent Had a minimum score of 20 or higher on the HAM-A at screening and baseline Had a minimum score of 2 on both the HAM-A item 1 (anxious mood) and item 2 (tension) at screening and baseline. Had a maximum score of 15 on the 17-item HAMD at screening and baseline visits.	
99815	Males and females between 18-65 years of age at baseline Had a primary diagnosis of GAD according to the DSM-IV-TR criteria (300.02) Written informed consent Had a score of 20 or higher on the HAM-A at screening and baseline Had a score of ≥2 on both the HAM-A item 1 (anxious	Female of childbearing potential who: had a positive pregnancy test at the screening visit, was without adequate contraception, was pregnant or breastfeeding. Met the DSM-IV-TR criteria for, or it was considered the predominant disorder within the previous 6 months (the MINI was used to confirm presence/absence of these disorders: Major Depressive Disorder, Panic Disorder, Social Anxiety Disorder, Posttraumatic Stress Disorder, Bipolar Disorder, Obsessive Compulsive Disorder, eating disorders (bulimia or anorexia), Body Dysmorphic Disorder, substance use disorder, any personality disorder that could jeopardise the evaluation of the treatment for primary GAD, as judged by the investigator. At risk of suicide (investigator's judgement) or had a score >3 points on

[9] This was not available at the time of the submission.

Trial ID	Inclusion criteria	Exclusion criteria
	mood) and item 2 (tension) at screening and baseline. Have a MADRS total score of 16 or lower at screening and baseline visits. Otherwise healthy (in the investigators opinion), based on a physical examination, medical history, ECG and the results of blood biochemistry and haematology tests carried out at screening visit. Willing and able to attend study appointments in the correct time windows	item 10 of the MADRS, or had made a serious suicide attempt within the past year Had an unstable serious illness and/or serious sequelae of: liver or renal insufficiency, or cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurological, infectious, neoplastic, or metabolic disturbance Used/had used any disallowed therapies (within 2 weeks prior to screening visit): psychoactive substances anxiolytics antidepressants (5 weeks for fluoxetine) monoamine oxidase inhibitors and reversible monoamine oxidase inhibitors benzodiazepines beta-blockers tryptophan oral antipsychotics depot antipsychotics (within 6 months, not 2 weeks) narcotic analgesics, warfarin sodium, digitalis, cardiac glycosides, type 1c antiarrhythmics, phenytoin or cimetidine regular daily therapy with any hypnotic except zolpidem psychoactive herbal remedies (e.g. St Johns Wort, Kava Kava, Valerian) antiepileptics ongoing prophylactic treatment with lithium, valproate or carbamazepine (to be stopped within 2 weeks prior to screening) triptans investigational drug (within 6 months, not 2 weeks) Required ECT or had received ECT within 6 months prior to the screening visit Receiving cognitive behavioural therapy, cognitive therapy, or problem-solving treatment or planned to initiate such therapy History of severe drug allergy or hypersensitivity, or a known allergy or hypersensitivity to citalopram, escitalopram or paroxetine. Had previously failed to respond to an adequate dose and duration of treatment with SSRIs or SNRIs. Unable or unlikely to follow the study protocol (investigators opinion)
99769	Males and females between 18-65 years of age at baseline Had a primary diagnosis of GAD according to the DSM-IV-TR criteria (300.02) Written informed consent Had a score of 20 or higher on the HAM-A at screening and baseline Had a score of ≥2 on both the HAM-A item 1 (anxious mood) and item 2 (tension) at screening and baseline. Have a MADRS total score of 16 or lower at screening and baseline visits. Otherwise healthy (in the	Female of childbearing potential who: had a positive pregnancy test at the screening visit, was without adequate contraception, was pregnant or breastfeeding. Met the DSM-IV-TR criteria for, or it was considered the predominant disorder within the previous 6 months (the MINI was used to confirm presence/absence of these disorders: Major Depressive Disorder, Panic Disorder, Social Anxiety Disorder, Posttraumatic Stress Disorder, Bipolar Disorder, Obsessive Compulsive Disorder, eating disorders (bulimia or anorexia), Body Dysmorphic Disorder, substance use disorder, any personality disorder that could jeopardise the evaluation of the treatment for primary GAD, as judged by the investigator, any psychotic disorder as defined in DSM-IV-TR, current or history thereof At risk of suicide (investigator's judgement) or had a score >3 points on item 10 of the MADRS, or had made a serious suicide attempt within the past year Had an unstable serious illness and/or serious sequelae of: liver or renal insufficiency, or cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurological, infectious, neoplastic, or metabolic disturbance Used/had used any disallowed therapies (within 2 weeks prior to screening

Trial ID	Inclusion criteria	Exclusion criteria
	investigators opinion), based on a physical examination, medical history, ECG and the results of blood biochemistry and haematology tests carried out at screening visit. Willing and able to attend study appointments in the correct time windows	visit): psychoactive substances anxiolytics antidepressants (5 weeks for fluoxetine) monoamine oxidase inhibitors and reversible monoamine oxidase inhibitors benzodiazepines beta-blockers tryptophan oral antipsychotics depot antipsychotics (within 6 months, not 2 weeks) narcotic analgesics, warfarin sodium, digitalis, cardiac glycosides, type 1c antiarrhythmics, phenytoin or cimetidine regular daily therapy with any hypnotic except zolpidem psychoactive herbal remedies (e.g. St Johns Wort, Kava Kava, Valerian) antiepileptics ongoing prophylactic treatment with lithium, valproate or carbamazepine (to be stopped within 2 weeks prior to screening) triptans investigational drug (within 6 months, not 2 weeks) any product that may stimulate serotonergic transmission (e.g. tramadole or sibutramine) Required ECT or had received ECT within 6 months prior to the screening visit Receiving cognitive behavioural therapy or psychotherapy or planned to initiate such therapy History of severe drug allergy or hypersensitivity, or a known allergy or hypersensitivity to citalopram, escitalopram or paroxetine.' Had been in a previous experimental study of escitalopram Had previously failed to respond to an adequate dose and duration of treatment with SSRIs or SNRIs. Unable or unlikely to follow the study protocol (investigators opinion)
Placebo versus benzodiazepine		
Hackett et al.	Male or female outpatient ≥18 years Meet DSM-IV criteria for GAD Written informed consent Had a score of 20 or higher on the HAM-A with a minimum score of 2 on the tension and anxiety items Had a Covi Anxiety Scale score which was greater than his/her Raskin Depression Scale (RDS) score and a total RDS score ≤9 Had a normal physical examination, laboratory test and ECG results from the screening visit or clinically insignificant abnormalities.	Met DSM-IV criteria for major depressive disorder in the previous 6 months History or presence of a mental disorder due to a general medical condition Experienced more than 2 panic attacks in the 4 weeks prior to the study RDS score >3 on 'verbal report' or 'behaviour' or >4 on 'secondary symptoms of depression' Concomitant use of other psychotropic medications, including antipsychotics, antidepressants, benzodiazepines and sedative-hypnotics (occasional chloral hydrate and zolpidem use permitted)

ECG = electrocardiogram, ECT = electroconvulsive therapy, HAM-A = Hamilton Anxiety Scale, HAMD = Hamilton Depression Scale, MINI = Mini International Neuropsychiatric Interview, MADRS = Montgomery and Åsberg Depression Rating Scale, RDS = Raskin Depression Scale, SSRI = selective serotonin reuptake inhibitor, SNRI = serotonin-noradrenaline reuptake inhibitor
Source – Study Reports:
SCT-MD-05 p. 25-28
SCT-MD-06 p. 24-27
SCT-MD-31 p. 2
99815 p. 24-26; 99769 p. 24-26
Hackett et al. p. 183

B.4.2 Trial dosage regimens

Studies SCT-MD-05, SCT-MD-6, SCT-MD-07 and SCT-MD-31 were flexible dose studies with the allowed doses described in Table B.4.3. The actual doses used in these flexible dose studies are detailed following Table B.4.3. Studies 99769 and 99815 used fixed doses of escitalopram (and placebo). Hackett et al. used fixed doses of diazepam (and placebo). The dosage regimens used in these clinical trials are fully described in Table B.4.3.

The Australian Approved Product Information (Attachment 1) for escitalopram use in GAD recommends commencing with 10mg daily, increasing to a maximum of 20mg daily if necessary. The study dosages reported are all within this approved range. The diazepam dosage in Hackett et al. was also within the recommended dosage range of 5-40mg daily (Valium (diazepam) Approved Product Information, Attachment 1).

Table B.4.3: Interventions compared by the randomised, controlled trials

Trial ID	Treatment	Dosage regimen	Duration of treatment (Median (range))	Duration of follow-up
Escitalopram vs placebo				
SCT-MD-05	ESC	Escitalopram 10mg daily[a] for 8 weeks[b]	56.0 days (1-89 days)[f]	NR
	Placebo	Placebo 1 tablet daily[a] for 8 weeks[b]	56.0 days (3-70 days)[f]	NR
SCT-MD-06	ESC	Escitalopram 10mg daily[a] for 8 weeks[b]	56.0 days (1-67 days)[f]	NR
	Placebo	Placebo 1 tablet daily[a] for 8 weeks[b]	56.0 days (1-67 days)[f]	NR
SCT-MD-07	ESC	Escitalopram 10mg daily[a] for 8 weeks[b]	56.0 days (1-77 days)[f]	NR
	Placebo	Placebo 1 tablet daily[a] for 8 weeks[b]	56.0 days (1-70 days)[f]	NR
SCT-MD-31[c]	ESC	Escitalopram 10mg daily[a] for 8 weeks[b]	56.0 (2.0, 77.0)[f]	NR
	Placebo	Placebo 1 tablet daily[a] for 8 weeks[b]	56.0 (6.0, 63.0)[f]	NR
99815[d,e]	ESC 5mg	Escitalopram 5mg daily for 12 weeks	88 days (4-105 days)[f]	NR
	ESC 10mg	Escitalopram 10mg daily for 12 weeks	89 days (1-108 days)[f]	NR
	ESC 20mg	Escitalopram 20mg daily for 12 weeks	91 days (1-121 days)[f]	NR
	Placebo	Placebo 1 tablet daily for 8 weeks	84 days (4-105 days)[f]	NR
99769[g]	ESC	Escitalopram 20mg daily[h] for 24 weeks	261 days (3-499 days)	NR
	Placebo	Placebo 1 tablet daily[h] for 24 weeks[i]	85 days (7-526 days)	NR
BZD vs placebo				
Hackett et al.[j]	Diazepam	Diazepam 15mg daily for 8 weeks	NR	NR
	Placebo	Placebo daily for 8 weeks	NR	NR

ESC = escitalopram, NR = not reported

a. the dose could be increased to 20mg daily or 2 placebo tablets after 4 weeks (1 week in SCT-MD-31) if a satisfactory therapeutic response had not been obtained.
b. Patients were to begin dosing on the evening of the baseline visit. Dosing could be switched to the morning, if preferred.
c. There was also a venlafaxine XR 75-225mg daily arm. Details are not reported in the submission as it is not a comparator.
d. There was also a paroxetine 20mg daily arm. Details are not reported in the submission as it is not a comparator.

e. Patients who completed double-blind treatment entered a 2-week (1 week double-blind then 1-week single-blind) washout period. At Week 12, half of the patients randomised to escitalopram 5 or 10mg/day (or 20mg/day paroxetine) received placebo during the 2-week washout period, while the other half continued active treatment for 1 week (Week 13) and received placebo for the second week (Week 14). Patients randomised to 20mg escitalopram were down-titrated to 10mg escitalopram for one week (Week 13) before they received placebo (Week 14).
f. Duration of treatment reported for the "All patients treated set" or safety population, i.e. all randomised patients who received at least one dose of study medication
g. As this was a relapse prevention study here was a 12-week initial open-label period with escitalopram (10mg/day in Week 1 and 20mg/day thereafter). Patients who responded in the open-label period were randomised into the 12 week double-blind period.
h. Preferably taken in the morning
i. During the double-blind period, patients randomised to placebo received 10mg/day escitalopram for 1 week and then continued on placebo
j. There were also venlafaxine XR 75 and 150mg mg daily arms. Details are not reported in the submission as it is not a comparator.

Source: Study Reports
SCT-MD-05 p. 29, Table 6.1
SCT-MD-06 p. 24, 28, Table 6.1
SCT-MD-07 p. 24, 28, Table 6.1
SCT-MD-31 p. 24, Table 6.1
99815 – p. 21, Table 13
99769 – p. 21, Table 32
Hackett et al. – p. 183

Studies 99769, 99815 used fixed doses of escitalopram (and placebo). Hackett et al. used fixed doses of diazepam (and placebo). The dosage regimens used in these clinical trials are fully described in Table B.4.3 above.

Studies SCT-MD-05, SCT-MD-6, SCT-MD-07 and SCT-MD-31 were flexible dose studies with the allowed doses described in Table B.4.3 above. The actual doses used in the studies are detailed below.

SCT-MD-05

Patients commenced the double-blind period of the study on escitalopram 10mg daily (or placebo). After Week 4 the dose could be increased to escitalopram 20mg daily (or 2 placebo tablets daily). The overall mean daily dose in the escitalopram group was 12.8mg or 1.28 tablets daily. The overall mean daily dose in the placebo group was 1.30 tablets daily. (Study Report p. 61, Table 6.3; calculated by dividing the total number of tablets or total mg by duration of treatment; reported for the Safety population)

SCT-MD-06

Patients commenced the double-blind period of the study on escitalopram 10mg daily (or placebo). After Week 4 the dose could be increased to escitalopram 20mg daily

(or 2 placebo tablets daily). The overall mean daily dose in the escitalopram group was 12.9mg or 1.29 tablets daily. The overall mean daily dose in the placebo group was 1.29 tablets daily. (Study Report p. 59, Table 6.3; calculated by dividing the total number of tablets or total mg by duration of treatment; reported for the Safety population)

SCT-MD-07

Patients commenced the double-blind period of the study on escitalopram 10mg daily (or placebo). After Week 4 the dose could be increased to escitalopram 20mg daily (or 2 placebo tablets daily). The overall mean daily dose in the escitalopram group was 12.3mg or 1.23 tablets daily. The overall mean daily dose in the placebo group was 1.31 tablets daily. (Study Report p. 59, Table 6.3; calculated by dividing the total number of tablets or total mg by duration of treatment; reported for the Safety population)

SCT-MD-31

Patients commenced the double-blind period of the study on escitalopram 10mg daily (or placebo). After Week 1 the dose could be increased to escitalopram 20mg daily (or 2 placebo tablets daily). The overall mean daily dose in the escitalopram group was 15.8mg or 1.85 capsules daily. The overall mean daily dose in the placebo group was 2.04 capsules daily. (Study Report p. 329, Table 6.2; reported for the Safety population)

B.4.3 Study designs

The efficacy and safety of escitalopram compared with placebo in GAD was investigated in six placebo-controlled clinical studies conducted as part of a comprehensive clinical development program:

Four eight-week flexible dose (10-20mg/day) studies - **Study SCT-MD-05, SCT-MD-06, SCT-MD-07, SCT-MD-31**

A 12-week fixed dose study (10mg or 20mg/day) – **Study 99815**

A 24-week flexible dose relapse prevention study – **Study 99769**

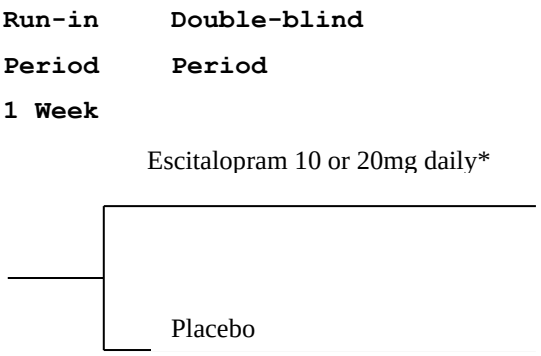
The designs of the different studies that compare escitalopram and placebo are presented below. In addition, study design details of the study by Hackett et al.[4] comparing placebo and diazepam (utilised in the indirect comparison of escitalopram and benzodiazepines) is also presented (Section d))

a) Eight-week flexible dose (10-20mg/day) studies comparing escitalopram and placebo (Study SCT-MD-05, SCT-MD-06, SCT-MD-07, SCT-MD-31)

These studies were multinational, randomised, double-blind, parallel-group, placebo controlled flexible-dose trials. There was a one-week single-blind run-in period with placebo, followed by an 8-week, double-blind treatment period with escitalopram or placebo. The initial dose of escitalopram was 10mg daily. At Week 4, 6 or 8 (or from Week 1-7 in Study SCT-MD-31) investigators had the option of doubling a patient's dosage of escitalopram (or placebo) from 10 to 20mg daily if his/her response had been unsatisfactory. Investigators could decrease the dosage to the original dosage at any time after the increase in dosage if there was an adverse event necessitating a dosage reduction.

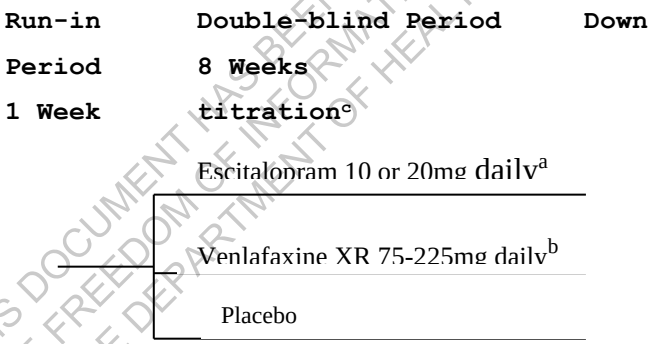
The overall study design for Study SCT-MD-05, SCT-MD-06 and SCT-MD-07 is presented in Figure B.4.1. The study design for SCT-MD-31 is presented in Figure B.4.2. In this study there was also a venlafaxine XR treatment arm and a down-titration run-out period. As venlafaxine is not a relevant comparator, information on this treatment arms is not presented in the submission

Figure B.4.1: Overall study design (Study SCT-MD-05, SCT-MD-06, SCT-MD-07)



* All patients were dosed with 10mg/day at the start of the double-blind period. The dose could be increased to 20mg/day at Week 4 or Week 6

Figure B.4.2: Overall study design (Study SCT-MD-31)



a. The escitalopram dosage could be increased to a maximum of 20mg/day at weekly intervals from Weeks 1-7.
b. The venlafaxine dosage could be increased to by 75mg/day at weekly intervals to a maximum of 225mg/day from Weeks 1-7
c. There was also a 2-week down titration period for patients who completed the study

Rationale for study design:

A double-blind, placebo-controlled design is the 'gold standard' design for investigating the efficacy and safety profile of a compound for this type of indication. The treatment duration of 8 weeks was chosen since clinically and statistically significant improvements in GAD have been seen with other SSRIs within an 8-week treatment period. Montgomery et al.[6] recommend in the European College of

Neuropsychiatry (ECNP) Guidelines for investigating efficacy in GAD that a study duration of 8 weeks in placebo-controlled studies has generally been successful and the number of early discontinuations has not compromised the duration of efficacy. Thus, the ECNP Guidelines for investigating efficacy in GAD (2000) recommend that efficacy studies in GAD should have a minimum duration of 8 weeks[6].

The dose of 10-20mg/day of escitalopram was chosen as this dose had been shown to have a broad spectrum of anxiolytic activity, and in addition efficacy in major depression, panic disorder and Social Anxiety Disorder has already been established[1]. The dose used is consistent with the dose in the Escitalopram Approved Product Information (Attachment 1). A placebo run-in period allowed both the opportunity to exclude patients who responded to placebo therapy to be excluded and also to washout psychoactive medication that had been taken prior to screening and which may influence social behaviour. The one-week duration also provided time for assessment of laboratory test results and ECGs.

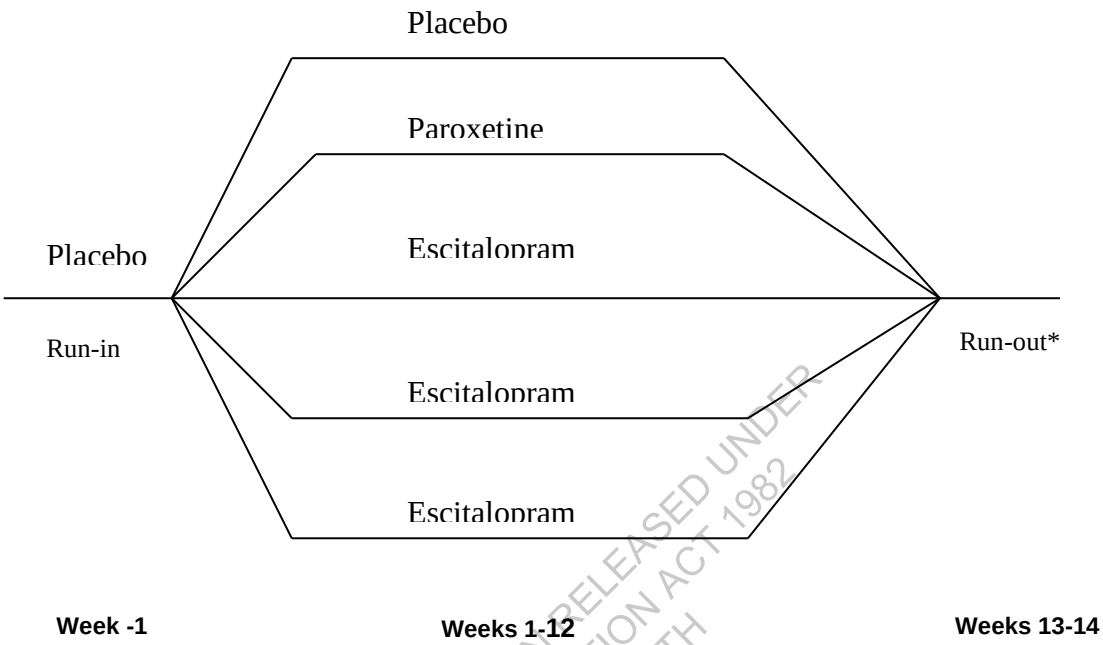
b) Twelve-week fixed dose study comparing escitalopram 10mg or 20mg/day with placebo (Study 99815)

This was a multicentre, fixed-dose, randomised, double-blind, placebo-controlled, active-reference study with five parallel treatment groups. The study consisted of a 1-week single-blind placebo run-in period after which patients were randomised to 12 weeks of double-blind treatment with fixed doses of escitalopram (5, 10 or 20mg/day), paroxetine (20mg/day) or placebo. The paroxetine arm results are not presented in this submission as it is not a comparator. The escitalopram 5mg daily treatment results are also not presented, as this is not a TGA-approved dosage for GAD in Australia.

Patients receiving escitalopram 5 or 10mg/day or paroxetine who completed double-blind treatment entered a 2-week single-blind run-out period during which half were randomised to receive placebo and half were randomised to receive active treatment for one week followed by placebo the next week.

The overall study design is presented in Figure B.4.3.

Figure B.4.3: Overall study design (Study 99815)



* Patients receiving escitalopram 5 or 10mg/day or paroxetine who completed double-blind treatment entered a 2-week single-blind run-out period during which half were randomised to receive placebo and half were randomised to receive active treatment for one week followed by placebo the next week.

Rationale for study design:

In line with the recommendation in the ECNP Guidelines[6], a placebo-controlled, fixed-dose design comparing three fixed doses of escitalopram to placebo was chosen to establish the optimal dose of escitalopram in the treatment of GAD. A duration of 12 weeks for the double-blind treatment period was chosen, since acute efficacy has been demonstrated after 8-12 weeks of treatment with paroxetine or venlafaxine in GAD studies (Study Report p. 22). Some patients respond to treatment within 8 weeks, while others responded more slowly (according to ECNP Guidelines[6]).

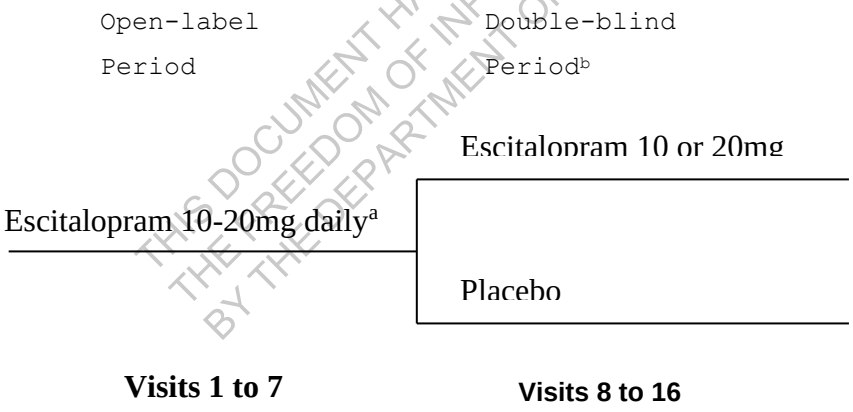
A one-week, single-blind, placebo run-in period was included to allow for the washout of previous psychoactive treatment, and to allow time for the assessment of clinical laboratory tests results and electrocardiogram (ECG) recordings. A two-week, run-out period was included to examine potential treatment withdrawal reactions.

c) Twenty-four week flexible-dose relapse prevention study (Study 99769)

This multinational, multicentre study consisted of a 12-week open-label period with flexible doses of escitalopram and a 24-week randomised, double-blind, parallel-group, fixed dose comparison of escitalopram and placebo in the prevention of relapse of GAD. Patients were in the double-blind period for a minimum of 24 weeks and a maximum of 76 weeks, depending on when in the accrual period they entered the study, as all patients were to complete the double-blind period simultaneously.

Throughout the double-blind period the investigators evaluated relapse symptoms. Relapse was defined either as an increase in HAM-A total score to 15 or more or an unsatisfactory treatment effect (lack of efficacy), as judged by the investigator. The overall study design is presented in Figure B.4.4.

Figure B.4.4: Overall study design (Study 99769)



a. All patients were dosed with 10mg/day at study start. The dose could be increased to 20mg/day at Week 2, 4 or 8.
b. After completion of the study patients were down-tapered using placebo in the placebo group, and one week of escitalopram 10mg/day and one week of placebo in the escitalopram group.
c. The patients remained on the dose to which they responded during the open-label period.
d. Response was defined as a score of 1 or 2 (*very much* or *much improved*) on the CGI-I scale. Non-responders left the study.

Rationale for study design:

In line with ECNP Guidelines[6], a relapse-prevention design, in which responders to an acute treatment period are randomised to double-blind, placebo-controlled treatment

(after down-tapering the dose), was chosen to establish the efficacy of escitalopram in relapse-prevention and in long-term treatment.

Considering the severity of the illness at inclusion and the response criterion, 12 weeks of treatment with escitalopram was judged a suitable duration for the open-label period. The double-blind treatment period of at least 24 weeks gave the opportunity to evaluate the long-term treatment effect.

The HAM-A, the standard scale for measuring severity of illness in patients with GAD, was used to measure the severity of illness at inclusion and the response to treatment at randomisation. In addition, HAM-A was used in the assessment of relapses. A HAM-A total score $\leq$10 was used as the response criterion, as it corresponds to at least a 50% reduction of the score on the pivotal scale at inclusion[6]. According to the Guideline, the relapse criterion should be defined between moderate severity and remission, thus a HAM-A total score of 15 or more was considered appropriate.

Source: Study Report p. 21-22

d) An eight-week fixed dose comparison of placebo and diazepam (Hackett et al.)
Hackett et al.[4] compares the use of placebo and benzodiazepine (diazepam). The results of this study are utilised to make an indirect comparison of escitalopram with benzodiazepines (using placebo as the common comparator). Hackett et al.[4] is available as a published paper only, meaning that the available details are more limited than those for the escitalopram versus placebo studies that are available as Study Reports.

The study is reported to be a multicentre, double-blind, randomised, placebo-controlled parallel group study comparing placebo, diazepam 15mg once daily, venlafaxine XR 75mg/day or venlafaxine XR 150mg/day for a period of eight weeks. The study was designed to compare the anxiolytic efficacy and safety of venlafaxine XR with that of diazepam in non-depressed outpatients with GAD.

B.4.4 Subject Characteristics in the randomised, controlled trials

Table B.4.4 presents the baseline characteristics of participants in the treatment arms in the six key direct randomised trials comparing escitalopram and placebo. Details of Hackett et al[4] comparing placebo and benzodiazepines is also presented. A comparison between the baseline characteristics of the escitalopram versus placebo studies and the placebo versus diazepam studies (i.e. the indirect comparison of escitalopram versus benzodiazepines) will be presented in Section B.4.5.

Subject characteristics in the treatments arms were generally similar, both within and across studies in the treatment studies (Study SCT-MD-06, SCT-MD-06, SCT-MD-07, SCT-MD-31, 99815). Baseline characteristics in the relapse prevention study (Study 99769) were similar between treatment groups within the study, but differed when compared with the treatment studies. The key subject characteristics are discussed below. The patients were outpatients, i.e. non-hospitalised at the time of recruitment.

Age, Sex, Race

Patients' mean age in the different treatment groups in the 6 studies ranged from 37-42 years. Generally, there was a lower percentage of males in the studies, ranging from 36-51% in all the treatment groups. Early onset GAD is reported is reported to have an equal gender distribution, but this separates sharply after the age of 20, when it becomes more common in females[6]. The majority of patients in all studies were Caucasian.

GAD onset, duration and treatment

GAD has a later age of onset, of a range from[7] 25 to 35 years[6 8] of age, compared with other anxiety disorders that usually start in adolescence. Patients in the treatment arms in the study had a mean age of onset of 27-31 years. This differed from the later age of onset reported in Study 99769 (relapse prevention study) where the mean age of onset in both groups was 37 years.

Mean duration of GAD ranged from 5-13 years. The duration of GAD was much shorter in Study 99769 (relapse prevention study) with a range of 4.6-5.5 years in the treatment groups, compared with the treatment studies (range 9-13 years). Less than half of patients in the treatment studies had previously received treatment for GAD (32-47%). In the relapse prevention study (Study 99769) 51-57% of patients had received prior therapy.

Level of impairment at baseline

The HAM-A total score at was used to assess the level of impairment of patients at baseline and the efficacy of therapy with active treatment. In the treatment studies patients mean HAM-A Total Scores at baseline ranged from 22-28, indicating that patients in the studies had moderate to severe GAD[6]. Patients in the three treatment groups in Study 99815 had higher mean HAM-A Total Scores than the other studies, a range of 26-28 compared with 22-24 in the other treatment studies (SCT-MD-05, SCT-MD-06, SCT-MD-07, SCT-MD-31). In the relapse prevention study, patients had a mean HAM-A Total Score of 27 prior to commencing open label escitalopram. At baseline immediately prior to randomisation the mean HAM-A score was 5-6, as by this time patients had received 12 weeks of open-label escitalopram therapy and only responders to therapy were randomised.

The baseline Hamilton Depression Rating Scale (HAMD) or Montgomery and Åsberg Depression Rating Scale (MADRS total score) was used to ensure that patients had a HAMD score of $\leq$15 or $\leq$17 in the different studies or MADRS score of $\leq$16. These depression rating scale scores were used to assess the level of depressive symptoms still present in the study population even though patients with major depressive disorder were excluded. Patients in all groups and studies demonstrated a low level of

depressive symptoms at baseline. In studies SCT-MD-05, SCT-MD-06, SCT-MD07 and SCT-MD-31 all patient groups had a mean HAMD score of <13. In Study 99815 the mean MADRS total score was <12. In Study 99269 the mean MADRS scores were <4, as patients had received 12 weeks of open-label escitalopram at baseline.

Table B.4.4: Baseline characteristics of participants in the randomised, controlled trials

Trial ID • Baseline characteristic	First randomised group	Second randomised group	Third randomised group	Fourth randomised group
Escitalopram vs placebo				
SCT-MD-05	Escitalopram	Placebo	P-value (ESC vs placebo)	
Mean age (years)	39.5	40.9	0.334	
Gender – n male (% male)	50 (40.3)	48 (37.5)	0.491	
Race - n (%) Caucasian Black Asian Other	 109 (87.9) 7 (5.6) 2 (1.6) 6 (4.8)	 116 (90.6) 7 (5.5) 1 (0.8) 4 (3.1)	0.442	
Mean BMI (kg/m²)[a]	27.5	26.7	Weight p=0.056 Height p=0.094	
Mean duration of GAD (years)	11.3	13.1	0.239	
Mean age of onset of GAD (years)	28.1	27.7	0.902	
Previous GAD treatment (n (%))	47 (37.9)	57 (44.5)	0.240	
Mean HAM-A Total Score (SD)	22.8 (3.58)	22.1 (3.71)	0.115	
Mean HAMD Total Score (SD)	11.8 (3.47)	12.0 (3.23)	0.670	
SCT-MD-06	Escitalopram	Placebo	P-value (ESC vs placebo)	
Age	36.8	38.4	0.260	
Gender – n male (% male)	56 (39.2)	70 (50.7)	0.055	
Race - n (%) Caucasian Black Asian Other	 111 (77.6) 8 (5.6) 6 (4.2) 18 (12.6)	 107 (77.5) 9 (6.5) 4 (2.9) 18 (13.0)	0.879	
Mean BMI (kg/m²)[a]	25.9	26.8	Weight p=0.048 Height p=0.088	
Mean duration of GAD (years)	9.76	9.49	0.839	
Mean age of onset of GAD (years)	27.0	28.9	0.233	
Previous GAD treatment (n (%))	55 (38.5)	51 (37.0)	0.830	
Mean HAM-A Total Score (SD)	22.6 (3.44)	22.6 (3.50)	0.908	

Trial ID • Baseline characteristic	First randomised group	Second randomised group	Third randomised group	Fourth randomised group
Mean HAMD Total Score (SD)	12.9 (2.63)	12.8 (2.43)	0.347	
SCT-MD-07	Escitalopram	Placebo	P-value (ESC vs placebo)	
Age	39.5	39.5	0.881	
Gender – n male (% male)	73 (47.4)	71 (46.4)	0.881	
Race - n (%) Caucasian Black Asian Other	 109 (70.8) 16 (10.4) 11 (7.1) 18 (11.7)	 110 (71.9) 15 (9.8) 8 (5.2) 20 (13.1)	0.736	
Mean BMI (kg/m²)[a]	26.9	27.3	Weight p=0.824 Height p=0.437	
Mean duration of GAD (years)	10.74	8.90	0.137	
Mean age of onset of GAD (years)	28.8	30.6	0.350	
Previous GAD treatment (n (%))	60 (39.0)	52 (34.0)	0.403	
Mean HAM-A Total Score (SD)	23.6 (4.6)	23.2 (4.2)	0.304	
Mean HAMD Total Score (SD)	12.4 (3.6)	11.9 (3.7)	0.077	
SCT-MD-31	Escitalopram	Placebo	P-value (ESC vs placebo	
Age	38.1	37.4	0.753	
Gender – n male (% male)	45 (36.0)	50 (37.0)	0.630	
Race - n (%) Caucasian Black Asian Other	 92 (73.6) 11 (8.8) 4 (3.2) 18 (14.4)	 104 (77.0) 12 (8.9) 5 (3.7) 14 (10.4)	0.632	
Mean BMI (kg/m²)[a]	27.3	26.8	Weight p=0.061 Height p=0.318	
Mean duration of GAD (years)	10.19	10.28	0.731	
Mean age of onset of GAD (years)	27.1	28.0	0.731	
Previous GAD treatment (n (%))	46 (36.8)	43 (31.9)	0.839	
Mean HAM-A Total Score (SD)	24.2 (4.0)	23.7 (3.2)	0.319	
Mean HAMD Total Score (SD)	11.5 (2.9)	11.8 (2.6)	0.293	

Trial ID • Baseline characteristic	First randomised group	Second randomised group	Third randomised group	Fourth randomised group
99815[b]	Escitalopram 10mg (n=136)	Escitalopram 20mg (n=133)	Placebo (n=139)	P-value (vs placebo
Mean age (years)	41.8	41	41.8	
Gender – n male (% male)	45 (33.1)	41 (30.8)	46 (33.1)	NR
Race - n (%) Caucasian Black Asian Other	 135 (99.3) 0 (0) 0 (0) 1 (0.7)	 131 (98.5) 2 (1.5) 0 (0) 0 (0)	 138 (99.3) 0 (0) 1 (0.7) 0 (0)	NR
Mean weight (kg)	70.4	69.4	73.2	NR
Mean BMI (kg/m²)	24.5	24.4	25.4	NR
Mean duration of GAD (years)	NR	NR	NR	NR
Mean age of onset of GAD (years)	NR	NR	NR	NR
Previous GAD treatment (n (%))	53 (39.0)	62 (46.6)	62 (44.6)	NR
Mean HAM-A Total Score (SD)	26.0 (4.1)	27.7 (4.9)	27.1 (4.6)	NR
Mean MADRS Total Score (SD)	11.0 (3.1)	11.4 (3.0)	11.4 (3.2)	NR
99769[b]	Escitalopram (n=187)	Placebo (n=188)	P-value (ESC vs placebo	
Mean age (years)	41.2	41.6	NR	
Gender – n male (% male)	75 (40.1)	76 (40.4)	NR	
Race - n (%) Caucasian Black Asian Other	 187 (100) 0 (0) 0 (0) 0 (0)	 183 (97.3) 2 (1.1) 1 (0.5) 2 (1.1)	NR	
Mean weight (kg)	73.8	73	NR	
Mean BMI (kg/m²)	25.5	25.3	NR	
Mean duration of GAD (years)	4.6	5.5	NR	
Mean age of onset of GAD (years)	37.2	36.6	NR	
Previous GAD treatment (n (%))	106 (56.7)	96 (51.1)	NR	
Mean HAM-A Total Score prior to open-label ESC	27.3 (4.4)			
Mean HAM-A Total Score at Baseline prior to randomisation (SD)	5.7 (2.9)	5.0 (3.1)	NR	
Mean MADRS Total Score (SD)	3.5 (2.7)	3.3 (2.7)	NR	

Trial ID • Baseline characteristic	First randomised group	Second randomised group	Third randomised group	Fourth randomised group
placebo vs benzodiazepine				
Hackett et al	Placebo	Diazepam 15mg	P-value (diazepam vs placebo)	
Mean age (years)	43	44	NR[c]	
Gender – n male (% male)	NR (36)	NR (36)	NR[c]	
Race - n (%) Caucasian Black Asian Other	 NR NR NR NR	 NR NR NR NR	NR	
Mean weight (kg)	NR	NR	NR	
Mean BMI (kg/m²)	NR	NR	NR	
Mean duration of GAD (years)	NR	NR	NR	
Mean age of onset of GAD (years)	NR	NR	NR	
Mean duration of **current** GAD episode (years)	6.4	6.0	NR[c]	
Previous anxiolytic treatment[d] - %	39%	39%		
Mean HAM-A Total Score (SD)	27.6	28.4		

ESC = escitalopram, GAD = General Anxiety Disorder, NR = not reported

a. BMI calculated from height and weight information provided in Study Report tables. The height and weight measurements provided in imperial in the Study Reports were converted to metric using the National Measurement Institute conversion chart found at http://www.measurement.gov.au/index.cfm?event=conversions

b. All data are for the 'all patients treated' (APTS) population, i.e. all randomised patients who took at least one dose of double-blind study medication (also called the "Safety Population"). Baseline data refers to Baseline II, i.e. immediately prior to randomisation, after receiving open-label escitalopram

c. Hackett et al. states that "There were no significant differences between the treatment group with respect to demographic data and the four treatment groups were similar in terms of prior psychotropic medication use" (p. 183)

Study Report reference:
SCT-MD-05 – Table 2.2, 2.4, 2.5
SCT-MD-06 – Table 2.2, 2.4, 2.5
SCT-MD-07 – Table 2.2, 2.4, 2.5
SCT-MD-31 – Table 2.1B, 2.2B. 2.5
99815 – Table 5, 6, 10, 16, 93
99769 – Table 12, 16, 20, 22, 97, 138
Hackett et al. p. 184

B.4.5 Characteristics of the randomised trials utilised in the indirect comparison of escitalopram and benzodiazepines

Hackett et al. compared the use of placebo and benzodiazepine (diazepam). There was limited information on the baseline characteristics of patients in Hackett et al., making comparisons with the escitalopram versus placebo studies difficult (Table B.4.4). The mean age of patients in this study (43-33 years) was similar to the escitalopram versus placebo studies. Mean HAM-A total scores at baseline were 28 in both treatment groups, indicating moderate to severe GAD. These HAM-A Total Scores were slightly higher than the escitalopram versus placebo treatment studies and similar to the relapse prevention study. Information is not provided on the duration or age of onset of GAD, only on the current GAD episode duration.

B.4.6 Subject characteristics in the non-randomised, open-label extension study

Selection of the Study Population

Details of the eligibility criteria for patients in the open-label extension study SCT-MD-17 are provided in Table B.4.5. Patients who had completed Study SCT-MD-05, SCT-MD-06 or SCT-MD-07 were eligible to enter into this open-label extension study.

Table B.4.5: Eligibility criteria in the non-randomised, open-label extension study (SCT-MD-17)

Inclusion criteria	Exclusion criteria
Male or female outpatient between 18-81 years Have a current diagnosis of GAD Written informed consent Have completed SCT-MD-05, SCT-MD-06 or SCT-MD-07 within 72 hours prior to study entry Must have physical examination, laboratory test and ECG results from the final visit of SCT-MD-05, SCT-MD-06 or SCT-MD-07 that are normal, or abnormalities clinically insignificant as judged by the investigator and documented in the case report form	Pregnant or breastfeeding women or women of childbearing potential not practising a reliable method of birth control. Met DSM-IV criteria for: Bipolar Disorder; Schizophrenia or any Psychotic Disorder; Obsessive Compulsive Disorder; Mental Retardation or any Pervasive Development Disorder or Cognitive Disorder. Principal diagnosis meeting DSM-IV criteria for any Axis I disorder other than GAD Personality Disorder of sufficient severity to interfere with their participation in the study History of any Psychotic Disorder, as defined by DSM-IV Any psychotic features At suicide risk, or who had made a serious suicide attempt within one year prior to the start of the study Met DSM-IV criteria for Substance Abuse or Dependence (other than nicotine) within six months prior to the study start Any malignancy (other than excised basal cell carcinoma) or any clinically significant haematological, endocrine, cardiovascular, renal, hepatic, gastrointestinal or neurological disease. Patients with such histories who had been stable for at least one year prior to the start of the study and judged by the investigator not to interfere with the patient's participation in the study. Systolic blood pressure greater than 180 mm Hg or less than 90 mm Hg or diastolic blood pressure greater than 105 mm Hg or less than 50 mm Hg at the screening or baseline visits. Treated with a depot neuroleptic within 6 months prior to study entry Treated with any neuroleptic, antidepressant or anxiolytic medication within 2 weeks (5 weeks for fluoxetine) prior to the first administration of double-blind study medication. Had received regular daily therapy with any benzodiazepine within one month prior to the first administration of double-blind study medication. Required concomitant treatment with any psychotropic drug (except zolpidem for sleep) or any drug with a psychotropic component Required concomitant therapy with any prohibited prescription or over-the-counter medication Had been in an investigational study within 1 month prior to study entry or who had received treatment with an investigational drug within 1 month or 5 half-lives, whichever was longer. Had participated in an investigational drug study for the treatment of depression within one year prior to study entry Had been in a previous investigational study of escitalopram Allergy or hypersensitivity to citalopram Had previously failed to respond to an adequate trial of citalopram or to adequate trials of two other SSRIs. Required ECT or had received ECT within 3 months prior to study entry Would require behaviour therapy or psychotherapy during the study Tested positive for alcohol, illicit drugs, or any prohibited medication on the urine drug screen Employees or relative of employees of the investigational site Unable to speak, read and understand English or who were judged by the investigator to be unable or unlikely to follow the study protocol. Not suitable for the study (in the opinion of the investigator)

ECG = electrocardiogram, SSRIs = selective serotonin reuptake inhibitors

Trial dosage regimen

Patients received escitalopram 10mg daily for the first four weeks. From Weeks 5-24 patients who had not exhibited a satisfactory therapeutic response in the opinion of the investigator were prescribed 20mg of escitalopram daily. Patients exhibiting a satisfactory response or those unable to tolerate 20mg per day continued to take 10mg daily.

For study completers the mean duration of treatment was 171 days. The mean daily dose taken was 13.4 mg/day (Study Report p. 51).

Study design

This was an open-label, multi-centre, flexible-dose extension study of 24 weeks duration. All patients received escitalopram therapy.

Subject characteristics

The baseline characteristics of patients in SCT-MD-17 are presented in Table B.4.6.

Table B.4.6:Baseline characteristics of patients in the non-randomised, open-label extension study (SCT-MD-17)

Baseline characteristic	Escitalopram
Age (years)	39.8
% Male - n (%)	244 (46.4)
Caucasian – n (%)	409 (77.8)
HAM-A Total Score – mean ± SEM	13.1 ± 0.3

SEM = standard error of the mean
Data is for the Safety Population (N=526), except HAM-A Total Score which is reported for the ITT population (N=121)
Source: Study Report p. 47-48

Source documents

Details of the source documents (Study Reports or published paper) with page or table references are provided under each submission table.

B.5 Outcome measures and analysis of the direct randomised trials

The primary and secondary outcomes for the seven key, randomised, controlled studies comparing escitalopram with placebo (comparator 1) and the study comparing the use of placebo and benzodiazepines (in order to provide an indirect comparison of escitalopram and benzodiazepines (comparator 2)) are presented, with details of primary outcomes, sample size calculations and statistical analyses. Details of the analyses undertaken, including a meta-analysis combining six key escitalopram versus placebo treatment studies is also presented.

Information on the primary and secondary outcomes, including the clinical importance of the outcomes measured in the studies is presented. s38

Changes in the HAM-A Total Score, psychic anxiety subscale and the individual items relating to anxious mood and psychic tension (that are particularly relevant to GAD) were measured in the studies and are reported in the meta-analysis and the individual study results in Section B.6.

The primary and secondary outcomes for the seven key studies are presented in Section B.5.1 and B.5.2. Full details of the analyses undertaken are provided, including a meta-analysis of the five of the six key trials that compare the use of escitalopram and placebo. The clinical importance of the outcomes measured in the trials is reviewed. The outcomes measured in the supportive non-randomised open-label extension study, including the analyses undertaken, are presented separately in Section B.5.4.

B.5.1 Primary outcomes

The primary outcomes, methods of statistical analysis and information on the sample size calculations in the seven randomised, controlled trials are presented in Table B.5.1 below.

Table B.5.1: Primary outcomes and statistical analyses of the randomised, controlled trials

Trial ID	Definition of primary outcome	Method of primary statistical analysis
Escitalopram versus placebo		
SCT-MD-05 SCT-MD-06 SCT-MD-07 SCT-MD-31[10]	Change from baseline to Week 8 in the HAM-A total score for ESC compared with placebo	Comparisons between ESC and placebo treatment were performed using an ANCOVA model with treatment (ESC and placebo) and study centre as factors, and the baseline score as a covariate. The analyses were performed using the LOCF approach. Power calculation A sample size of approximately 120 patients in each treatment group was required to detect an effect size of 0.4 (at least 40% of the standard deviation) with 85% power using a two-sided two sample t-test at an alpha level of 0.05.
99815	Change from baseline to Week 12 in the HAM-A total score	Comparisons between ESC and placebo treatment were performed using an ANCOVA model with treatment (ESC and placebo) and study centre as fixed factors, and the baseline score as a covariate. The analyses were performed using the LOCF approach. An F-test was used to test the overall null hypothesis of equal mean changes of the 3 ESC groups and the placebo group. If the overall F-test was significant at the 5% level, pairwise comparisons of each of the 3 ESC dose group mean changes and the placebo group mean change were made using two-sided t-tests with the overall mean square error (MSE) as an error term at a 5% level of significance. The appropriateness of the final model was evaluated by inspection and analysis of residuals, by comparing variability between treatment groups and the evaluating the potential influence of covariates. Power calculation A minimum of 130 patients in each treatment group (FAS) was required to detect an effect size of 0.35, i.e. a significant treatment difference to placebo of at least 35% of the pooled standard deviation when comparing the mean change from baseline to Week 12 (LOCF) in HAM-A total score using a two-sided t-test with 80% power at a 5% level of significance.

[10] This was not available at the time of the submission.

Trial ID	Definition of primary outcome	Method of primary statistical analysis
99769	Time to relapse (days) for ESC compared with placebo. Relapse was defined as either: An increase in the HAM-A total score to 15 or more, or An unsatisfactory treatment effect (lack of efficacy), as judged by the investigator.	The primary analysis of efficacy was a two-tailed log-rank test comparing the time to relapse of GAD in the ESC group with that in the placebo group. This analysis was supplemented by Kaplan-Meier plots. The appropriateness and robustness of the analysis was studied by investigating the possible effect of centre and centre-by-treatment interaction. This was done by applying a stratified log-rank test, Cox's proportional hazard model and accelerated failure models, taking the interval-censored nature of the survival times into account. Power calculation The sample size and power calculations were based on the analysis of time to relapse in the double-blind period. The calculations assumed a length of accrual for the double-blind period and a treatment duration of at least 24 weeks. The calculation of power was based on a relapse hazard ratio of 0.47. This assumed a cumulative relapse rate at 24 weeks of 0.11 for the ESC group versus 0.23 for the placebo group. In addition, the calculation of power assumed that withdrawal due to other reasons would occur at a rate of 0.02 per month (4 weeks) in both treatment groups. Using these assumptions 125 patients per treatment group randomised to the double-blind period at an average rate of approximately 20 patients per month would provide 85% power to find a statistically significant difference between ESC and placebo, using a two-tailed, log-rank test at the 5% level of significance.
BZD versus placebo		
Hackett et al.	Adjusted mean change from baseline to week 8 for ESC compared with placebo in: HAM-A total score HAM-A psychic anxiety score HAD anxiety sub-scale score CGI-I rating	Analysis of continuous efficacy rating scales were conducted using ANCOVA with treatment, centre, and their interaction as factors and the baseline value as a covariate in the model. The adjusted means and the observed means with their 95% confidence limits were computed, as well as the pairwise differences of adjusted means with their 95% confidence limits. Responders on the HAM-A scale were defined as those patients showing a 50% or greater decrease from baseline in total score. Responders on the CGI-I scale were defined as those patients showing a score of 1 (very much improved) or 2 (much improved). The percentage of responders were analysed using logistic regression. The primary efficacy analysis was carried out using the LOCF method to impute missing data. Primary comparisons of interest were placebo against each dose venlafaxine XR at the Week 8 endpoint. Pairwise comparisons were considered significant when the P-values for the overall F-test was 0.05 and the pairwise was comparison was <0.025 (Bonferonni's correction). All tests of hypotheses were two sided.

ANCOVA = analysis of covariance, BZD = benzodiazepine, CGI-I = Clinical Global Impression – Improvement, ESC = escitalopram, FAS = full analysis set, HAD = Hospital Anxiety and Depression Scale, HAM-A = Hamilton Anxiety Scale, LOCF = last observation carried forward
Source: Study Reports
SCT-MD-05 p. 43, 50
SCT-MD-06 p. 42, 48
SCT-MD-07 p. 42, 48
SCT-MD-31 p. 27
99815 p.40, 44
99769 p. 33, 42, 43, 45
Hackett et al. p.183

B.5.2 Secondary outcomes

All secondary outcomes and the statistical analysis methods used in the seven direct randomised, controlled trials are presented in Table B.5.2 below.

The results of secondary outcomes not considered patient-relevant are not presented in this submission. See Section B.5.3.3 for a full listing of patient-relevant secondary outcomes that are reported in Section B.6 in this submission (and meta-analysed if sufficient data is available).

A full list of secondary outcomes that are not considered patient-relevant is also provided in Section B.5.3.3. The results of all secondary outcomes are available in the individual Study Reports provided.

Table B.5.2: Patient-relevant secondary outcomes and analyses in the direct randomised trials

Trial ID	Definition of secondary outcome	Method of statistical analysis
Escitalopram versus placebo		
SCT-MD-05 SCT-MD-06 SCT-MD-07 SCT-MD-31	Secondary outcomes: Change from Baseline to Week 8 for ESC compared with placebo in: CGI-S score HAM-A psychic anxiety subscale score CGI-I score Evaluation of the safety of ESC – including withdrawals, TEAEs Additional efficacy outcomes: Change from Baseline to Week 8 for ESC compared with placebo in: HAMD total score QOL total score Covi total score (not in SCT-MD-31) Raskin total score (not in SCT-MD-31) HAD anxiety subscale score HAD depression subscale score HAMD anxiety subscale score (not in SCT-MD-31) HAM-A somatic anxiety subscale score HAM-A anxiety item HAM-A tension item CGI-I response rate (CGI-I ≤2) (calculated) The following endpoints are in SCT-MD-31 only: HAM-A psychic item VASOVER score HAM-A response rate (HAM-A ≤10) HAM-A response rate (≥50% reduction from baseline) HAM-A remission rate (HAM-A ≤7)	Comparisons between ESC and placebo treatment were performed using an ANCOVA model with treatment (ESC and placebo) and study centre as factors, and the baseline score as a covariate. The analyses were performed using the LOCF approach. A two-way analysis of variance (ANOVA) model was used for the CGI-I score at Week 8, since this parameter, by definition, records improvement relative to baseline and is not measured at baseline. In SCT-MD-31 CGI-I at Week 8 was measured using an ANCOVA model with treatment group and study centre as factors and baseline CGI-S score as a covariate. In SCT-MD-31 remission and response rates were analysed using logistic regression with treatment group and the respective baseline values as explanatory variables.

Trial ID	Definition of secondary outcome	Method of statistical analysis
99815	Change from Baseline to each visit in: HAM-A total score HAM-A psychic anxiety subscale score HAM-A somatic anxiety subscale score HAM-A score for item 1 (anxious mood) HAM-A score for item 2 (tension) Proportion of responders (patients with a ≥50% reduction in HAM-A total score) Proportion of remitters (patients with a HAM-A total score ≤9 per visit[a]) Proportion of remitters (patients with a HAM-A total score ≤7 per visit[a] HAD anxiety score CGI-S score SDS (work, family life, social life) scores CGI-S score per visit CGI-I score per visit Proportion of responders (patients with a CGI-I score ≤2 per visit) Safety was evaluated on the basis of withdrawals, adverse events, DESS scale scores, vital signs and weight/BMI	The HAM-A total score per visit, the change from Baseline to each nominal visit in HAM-A psychic anxiety and somatic anxiety subscale scores, the HAM-A items 1 and 2 scores, the CGI-S score, HAD-A score and SDS (work, family life, social life) scores were analysed by ANCOVA with treatment and centre as fixed factors, and with baseline HAM-A score as a covariate. The CGI-I was analysed using ANOVA. The HAM-A item 1 and item 2 scores and CGI-S and CGI-I scores were also analysed at Week 12 using the non-parametric Cochran-Mantel-Haenszel (CMH) mean score statistic with modified ridit scores and with individual centres comprising the strata. Between group comparisons using Fisher's exact test were made for the proportion responders and remitters.
99769	Change from Baseline to each visit in: HAM-A total score HAM-A score for item 1 (anxiety mood) HAM-A score for item 2 (tension) HAM-A psychic anxiety subscale score HAM-A somatic anxiety subscale score HAD anxiety subscale score CGI-S score SDS subscale (work, family life, social life) scores CGI-I score per visit Safety was evaluated on the basis of withdrawals, adverse events	All secondary analyses were tabulated per visit using LOCF. All the LOCF tabulations were based on the first 24 weeks of the double-blind period to minimise the bias introduced by the difference in withdrawal rates and the differential exposure to study drug. The crude relapse rates were compared between treatment groups using a Chi-squared test. The influence of the potential effect of discontinuation symptoms on the primary analysis was investigated in 4 analyses in which relapses occurring during the first 7, 14, 21 or 28 days after randomisation were censored.
BZD versus placebo		
Hackett et al.	The following were evaluated in the randomised population (and not listed as primary endpoints): Safety assessments Use of concomitant medications Physical examinations Laboratory measurements Recording of adverse events Reasons for patient discontinuation	The incidence of adverse events and reasons for discontinuation were analysed using logistic regression

BMI = body mass index, CGI-I = Clinical Global Impression – Improvement, CGI-S = Clinical Global Impression – Severity, ESC = escitalopram, HAD = Hospital Anxiety and Depression Scale, HAM-A = Hamilton Anxiety Scale, HAMD = Hamilton Depression Rating Scale, LOCF = last observation carried forward, QOL = Quality of Life, Enjoyment and Satisfaction Questionnaire, VASOVER = Visual Analogue Scale for Overall Pain.
a. defined as an exploratory efficacy endpoint. The analysis was performed post-hoc based on the ECNP Guidelines[6] and the EU CPMP Guidelines
Source: Study Reports SCT-MD-05 p. 41, 44 ; SCT-MD-06 p. 43, 50; SCT-MD-07 p. 40, 41, 43; SCT-MD-31 p. 27, 28; 99815 – 40, 41; 99769 – p. 33, 36, 43; Hackett et al. – p. 183

B.5.3 Analysis of the trial data

A large number of primary and secondary outcomes have been analysed in the seven key studies. In addition, the results of patient-relevant outcomes in five of the six key studies comparing the use of escitalopram and placebo have been meta-analysed as described in Section B.5.3.2. The primary and patient-relevant secondary outcomes have been meta-analysed (if sufficient data is available) and reported in this submission.

B.5.3.1 Analysis of the individual studies

Escitalopram versus placebo

The method of analysis of the primary and secondary outcomes of the six key studies comparing escitalopram and placebo has been provided in Section B.5.2. A large number of clinical outcomes were assessed. The clinical importance of these outcomes is discussed in Section B.5.4.

Study SCT-MD-05, SCT-MD-06, SCT-MD-07 and SCT-MD-31 all had 8-week (double-blind) active treatment periods, while Study 99815 had a 12-week active treatment period. Results are reported at study endpoint (Week 12) and at Week 8 (where available, to allow comparison with the other treatment studies) for Study 99815. Relapse prevention Study 99769 has a 24-week double-blind period. Results are reported at Week 12 and 24.

The Clinical Study Reports contain results for mean change from baseline for the continuous outcomes (eg. HAM-A, SDS Scores) as well as adjusted mean change from baseline (using ANCOVA) for the same outcome. **Adjusted** mean change was specified in the analysis for the primary and secondary outcomes in some of the studies, these results are reported in the individual study results in Section B.6. The (unadjusted) change values are used for the meta-analysis. This can lead to slight differences in the values reported for some of the individual studies and in the study meta-analysis data.

Placebo versus benzodiazepines (diazepam)

Hackett et al. compares the use of placebo and benzodiazepines in DSM-IV diagnosed GAD patients. Table B.5.1 presents details of the analysis of the primary and other efficacy variables. Limited results data is provided in the published study, as much of the results and discussion is based on a post-hoc analysis of placebo-response rates at different treatment centres, rather than focussing on the pre-defined study outcomes that are relevant to this submission.

B.5.3.2 Meta-analyses undertaken

A meta-analysis combining the results of five of the six key studies comparing escitalopram with placebo (Study SCT-MD-05, SCT-MD-06, SCT-MD-07, SCT-MD-31, 99815) has been undertaken. See Attachment 6 for full details of study methodology and results. Some key issues in the design and conduct of the meta-analysis are highlighted below.

Excluded study (Study 99769)

Study 99769 has not been meta-analysed with the other five key studies comparing escitalopram with placebo. It is not possible to validly combine the results of the six direct comparative studies, due to significant differences in the objectives and design of Study 99769 compared with the other two key studies, leading to different patient populations being randomised to active treatment.

Study 99769 was a relapse prevention study. The trial was undertaken in order to determine the rate of patient relapse following successful treatment of GAD. All patients who met the eligibility criteria received open-label escitalopram for 12 weeks prior to study randomisation. Only patients who responded to therapy were randomised to continue in the relapse prevention study (since in order to be able to relapse, a patient must have responded to treatment). Thus the patients entering the randomised active treatment phase of this study were a “responder sub-population” of the patients with GAD who were initially eligible to enter the study. This is a different total patient population to that of the other escitalopram versus placebo

treatment studies. Due to the significant differences in the patient population randomised in Study 99769 (the relapse prevention study), compared with the other treatment studies, the results could not validly be combined in a meta-analysis.

Escitalopram treatment arms combined in the meta-analysis

Study 99815 was a fixed-dose study comparing three doses of escitalopram - 5mg, 10mg and 20mg daily – with placebo. The other treatment studies were flexible dose studies with patients taking escitalopram 10mg to 20mg daily or placebo. Patients in these studies took mean daily doses of 12.8mg, 12.9mg, 12.3mg and 15.8mg at Week 8. The meta-analysis combined the results of the fixed dose escitalopram 10mg and 20mg daily treatment arms in Study 99815 (individually with continuous data and combined with dichotomous data) with the flexible dose escitalopram arm in the other studies.

Treatment time-point analysed

Study 99815 had a 12 week active treatment phase. All of the other treatment studies were of 8 weeks duration. The 8 week outcome data for each of the studies, including where it was available for Study 99815, was combined in the meta-analysis. See Section B.6 for details of 12 week responses in Study 99815 and 12 and 24 week responses in Study 99769.

Sensitivity Analyses

Sensitivity analyses were conducted by removing individual studies from the meta-analysis and observing the effect on the results. Individual removal of studies from the pooled analyses with respect to the condition of GAD resulted in only three changes of statistical significance. An indirect analysis comparing the results from Hackett et al. with the escitalopram versus placebo studies was also conducted.

Indirect comparison of escitalopram and benzodiazepines

A statistical analysis comparing escitalopram and benzodiazepine via an indirect comparison (placebo) was also undertaken as part of the meta-analysis.

B.5.3.3 Outcomes analysed in the meta-analysis and/or individual studies and reported in Section B.6

There are a large number of secondary outcomes reported in the studies comparing escitalopram and placebo. Table B.5.3 lists the outcomes that have been meta-analysed and/or reported in the individual studies with the results presented in Section B.6 of the submission.

All study outcomes reported in the publication for the comparison of placebo and benzodiazepines (Hackett et al.[4]) are reported in Section B.6. However limited data is available due to the selected reporting of outcomes in that publication.

Table B.5.4 lists the study outcomes reported in the individual studies that have not been meta-analysed or reported in Section B.6, with reasons.

Table B.5.3: Patient-relevant outcome results reported in the escitalopram versus placebo studies Section B.6

Patient-relevant outcome Escitalopram vs placebo	Trial ID						
	Meta-analysis	**SCT-MD-05**	**SCT-MD-06**	**SCT-MD-07**	**SCT-MD-31**	**99815**	**99769**
Time-point analysed and reported	Week 8	Week 8	Week 8	Week 8	Week 8	Week 8 & 12	Week 12 & 24
Primary endpoints							
Change in mean HAM-A Total Score	√	√	√	√	√	√	√*
Time to relapse	NA	NA	NA	NA	NA	NA	√
Secondary efficacy endpoints							
Change in mean HAM-A response rate (>50% reduction in HAM-A Total Score	√	NR	NR	NR	√	√	NR
Percentage of patients with HAM-A≤7 (HAM-A remission rate)	√	NR	NR	NR	√	√	NR
Percentage of patients with HAM-A≤9 (HAM-A remission rate, alternative definition))	NA	NR	NR	NR	NR	√	NR
Change in mean HAM-A psychic anxiety subscale score	√	√	√	√	√	√	√
Change in mean HAM-A anxiety item	√	√	√	√	√	√	√
Change in mean HAM-A tension item	√	√	√	√	NR	√	√
Mean CGI-I score	√	√	√	√	√	√	NR
Percentage of patients with CGI-I≤2 (CGI-I responders)	√	√	√	√	√	√	NR
Change in mean CGI-S score	√	√	√	√	√	√	√
Change in mean HAD anxiety subscale score	√	√	√	√	√	√ Week 12	√
Change in mean QOL score	√	√	√	√	√	NR	NR
Change in mean HAMD Total Score	√	√	√	√	√	NR	NR
Secondary safety endpoints							
Total study withdrawals	√	√	√	√	√	√ Week 12	√ at endpoint
Study withdrawals - due to lack of efficacy	√	√	√	√	√	√ Week 12	√ at endpoint
Study withdrawals – due to AEs	√	√	√	√	√	√ Week 12	√ at endpoint

Patients with TEAEs	√	√	√	√	√	√ Week 12	√ at endpoint
TEAEs occurring in ≥5% of patients	√	√	√	√	√	√ Week 12	√ at endpoint

Key: √ = outcome reported in the Study Report or analysed in the meta-analysis and results presented in Section B.6; NA = not available – not a pre-defined study outcome, therefore data not collected; NR = not reported – data not reported for that outcome ; Changes are all change from baseline; AE = adverse events, CGI-I – Clinical Global Impression Improvement, CGI-S– Clinical Global Impression Severity, HAM-A = Hamilton Anxiety Scale, HAD = Hospital anxiety and depression scale, TEAE = treatment-emergent adverse events

Table B.5.4: Secondary outcome results that are not presented for the escitalopram versus placebo studies in Section B.6 (with reasons)

Secondary outcome Escitalopram vs placebo	Trial ID						Reason
	SCT-MD-05	SCT-MD-06	SCT-MD-07	SCT-MD-31	99815	99769	
Time-point analysed and reported	Week 8	Week 8	Week 8	Week 8	Week 8	Week 12 & 24	
Secondary efficacy endpoints							
Covi Total Score	√	√	√				Used as exclusion criteria Not a relevant endpoint as it measures depression
Raskin Total Score	√	√	√				
HAD depression subscale score	√	√	√	√			
HAMD anxiety subscale score	√	√	√	√	√	√	HAM-A psychic anxiety subscale scores reported, as more relevant
HAM-A somatic anxiety subscale score	√	√	√	√	√	√	HAM-A psychic anxiety subscale scores reported, as more relevant
HAM-A psychic item				√			More relevant HAM-A items reported (anxiety, tension)
VASOVER score				√			Not relevant
Proportion of patients with HAM-A≤10				√			Other HAM-A responder definitions presented.
Sheehan Disability Scale Subscale scores					√		Only reported in one study. Other outcome scales considered more relevant.
Secondary safety endpoints							
DESS scores						√	Not relevant

Key:
√ = results for this outcome available in the Study Report, however the results are not presented in Section B.6 for the reasons provided, AE = Adverse Events; CGI-I = Clinical Global Impression – Improvement; CGI-S = Clinical Global Impression, DESS = Discontinuation Emergent Signs and Symptoms' HAM-A = Hamilton Anxiety Scale, HAMD = Hamilton Depression Scale, MADRS = Montgomery and Åsberg Depression Rating Scale, SDS = Sheehan Disability Scale; TEAE = treatment-emergent adverse event.
VASOVER = Visual Analogue Scale for Overall Pain

B.5.4 Clinical importance of the outcomes used in the studies

Measurement scales

The Hamilton Anxiety Scale (HAM-A) (change in the Total Score) is the primary outcome in the treatment studies and a secondary outcome in the relapse prevention trial. According to the ECNP Guidelines[6] it has been used as the gold standard in clinical trials, though it does have shortcomings as it was not developed specifically to measure GAD. The core features of GAD according to DSM-IV are the nervous tension and chronic worrying. These psychic symptoms are captured in part in the HAM-A but the scale has an over-representation of autonomic symptoms. To address this, some studies have concentrated on specific items that contribute to the psychic anxiety factor as being more relevant to DSM-IV GAD. Anxious mood (item 1) and psychic tension (item 2) are most relevant.[6]

s38

Changes in the HAM-A Total Score, psychic anxiety subscale and the individual items relating to anxious mood and psychic tension were measured in the studies and are reported in the meta-analysis and the individual study results in Section B.6.

The anxiety subscale of the Hospital Anxiety and Depression Scale (HAD) may also capture the psychic anxiety aspects of GAD more directly, though experience with this scale in clinical trials is more limited[6]. The HAD anxiety subscale change results are also reported for the individual studies and the meta-analysis in Section B.6.

Responders and remitters

According the ECNP Guidelines[6] 50% reduction in HAM-A Total Score is a widely accepted criteria of response. Remission rate can be a useful measure of efficacy, particularly in long-term treatment studies. Measure of remission based on HAMA ≤10, ≤8 or ≤7. [6 9 10 11]

.

The HAM-A response rates, based on percentage of patients with a 50% reduction and a score of ≤7 are also presented in the meta-analysis and for the individual studies in which they are reported.

The CGI-I (improvement) and CGI-S (severity) have also been used for responder analyses, but the CGI-S is not a sensitive measure and CGI-I score of ≤2 (much or very much improved) is rather insensitive and tends to focus on recent change[6]. Change in percentage of CGI-I responders and CGI-S Score are reported in the meta-analysis and individual study results in Section B.6.

It would be reasonable to conclude that given that the sum (total score) indicates the severity of anxiety; and that HAM-A<12 is normal, then patients achieving this can be considered to be remitters.

Relapse

In relapse prevention studies (such as Study 99769) the most sensitive criterion of relapse appears to be the withdrawal of an individual from the placebo-controlled study for efficacy reasons[6]. This measure has the advantage of being independent of pivotal scales but lacks objectivity and consideration may be given to a prespecified increase on a severity scale to define an event. In Study 99769 the relapse criterion was an increase in the HAM-A score to ≥15 or a lack of efficacy as judged by the investigator. The results of this primary study outcome in Study 99769 are reported in Section B.6.

Summary

While the HAM-A is considered the gold standard scale in measuring GAD, there is no single, well-defined clinical outcome measure that alone is able to demonstrate overall clinical improvement in GAD. Instead improvement in a number of clinical outcome scales and sub-scales (including change in HAM-A Total Score, HAM-A psychic anxiety subscale, HAM-A responders, CGI-I responders, HAD anxiety subscale score) is used to demonstrate the benefits of pharmacotherapy at improving the psychic anxiety characteristic of GAD are presented.

B.5.5 Measurement scales used as primary and secondary outcomes in the studies

Hamilton Anxiety Scale (HAM-A)

This scale rates the patient's level of anxiety based on feelings of anxiousness, tension and depression; any phobias, sleep disturbance, or difficulty in concentrating, the presence of genitourinary, cardiovascular, respiratory, autonomic or somatic symptoms, and the interviewer's assessment of the patient's appearance and behaviour during the interview are also rated.

The HAMA was developed to quantify the severity of symptoms of anxiety and is widely used to evaluate anxiety in clinical studies. The Hamilton Anxiety Scale consists of 14 items, each defined by a series of symptoms; 1) anxious mood, 2) tension, 3) fears, 4) insomnia, 5) intellectual, 6) depressed mood, 7) somatic complaints: muscular, 8) somatic complaints: sensory, 9) cardiovascular symptoms, 10) respiratory symptoms, 11) gastrointestinal symptoms, 12) genitourinary symptoms, 13) autonomic symptoms, and 14) behaviour at interview.

Each item is rated on a 5-point scale, ranging from 0 (not present) to 4 (very severe). The sum (total score) indicates the severity of anxiety; less than 12 is normal, 18 mild anxiety (and the lowest threshold at which medication is usually prescribed), 25 moderate anxiety, and 30 severe anxiety.[12]

Typically in clinical trials response is determined for a ≥50% reduction in HAM-A and remission is defined by patients with a HAM-A<10 or a HAM-A<8[13], both of which is within the range of normal anxiety determined as HAM-A<12.[12]

Consensus conferences proposed that for GAD, remission is defined as HAM-A≤7-10 functional impairment is SDS≤1 on each item and a HAM-D score of ≤7.[10 11]

HAM-A Psychic Anxiety Subscale

The HAM-A psychic anxiety subscale is derived from the HAM-A scale and consists of the sum of the following items: item 1 (anxious mood), item 2 (tension), item 3 (fears), item 4 (insomnia), item 5 (intellectual), item 6 (depressed mood), and item 14 (behaviour at the interview).

Clinical Global Impression (CGI)

The CGI consists of two subscales:

- Clinical Global Impressions – Improvement scale (CGI-I):

This scale evaluates a patients total improvement from baseline I on a 7 point-scale, regardless of whether the improvement is related to the study product. The assessor rates the patient from 1 (*very much improved)* to 7 (*very much worse)*

- Clinical Global Impressions – Severity scale (CGI-S):

This scale evaluates a patient's severity of disease on a 7-point scale based on the investigators total clinical experience with this population. The assessor rates the patient from 1 (*normal, not at all ill*) to 7 (*among the most extremely ill patients*). (Source: 99815 Study Report p. 33)

Responders: CGI-I≤ 2 (much or very much improved)[13] or CGI-I ≥50% reduction[14]. These patients have improved but have not yet reached remission.

Remission:[13] CGI-S≤ 2 (normal, not at all ill, or borderline illness). This has been used to define remitters but the level of remission represented by these scores remains controversial.

When defining 'response' to a treatment on a standard rating scale, a ≥50% reduction of scale score this was found to be too conservative, with clinically measurable difference at a smaller change from baseline being found to be more accurate as can be seen in Table B.5.5.

Table B.5.5: Correlation of Response/Treatment Between Scales[14]

CGI Defined	Corresponding Reduction in HAM-A
Response CGI-I ≥50% reduction	42%
Remission CGI-S ≤2	9 points

Hamilton Depression Rating Scale

This 17-item scale rated the patient's depressive state based on feelings of depression, guilt, suicidality, anxiety (psychic and somatic), and agitation; level of insight; patterns of insomnia (early, middle, late); loss of interest in work and other activities; weight loss, hypochondriasis psychomotor retardation; genital symptoms, gastrointestinal somatic symptoms and general somatic symptoms. Each item was scored on 3-, 4- or 5-point scale with 0 reflecting no symptoms and higher scores reflecting increasing symptom severity.
(Source: SCT-MD-05 Study Report p. 16)

Hospital Anxiety and Depression Scale (HAD)

The HAD scale is completed by the patient and comprises two subscales: one that measures depression (D-scale) and one that measures anxiety (A-scale). Each subscale consists of seven items, with four possible response alternatives (scored from 0 to 3, with 0 reflecting the most enjoyment/least anxiety). The D-scale consists of HAD items 1, 3, 5, 8, 10, 11 and 13, and the A-scale consists of HAD items 2, 4, 6, 7, 9, 12 and 14. Patients fill in the scores that most accurately reflect the way they had felt over the previous days. Scores for the depression and anxiety subscales are calculated separately.
(Source: Study Report for 99815 p.33)

Montgomery and Åsberg Depression Rating Scale (MADRS)

The MADRS[15] consists of 10 items, each rated on a scale from 0 (*no symptoms*) to 6 (*severe symptoms*). All the items are core symptoms of a depressive episode and thus measure the severity of a depressive episode for the previous 7 days.

The symptoms rated are: apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts.

The MADRS is based on a clinical interview with the patient beginning with general questions about symptoms and gradually becoming more detailed to allow for a precise rating of depression severity.

The MADRS is included in some studies (with others using the HAMD) to determine that patients as a measure of depressive status, rather than an efficacy outcome.

Sheehan Disability Scale (SDS)

The SDS[16] is a 3-item scale to measure impairment. The items address the impact of symptoms of GAD on work, social life, and family life, within the last 7 days. The rating is based up an interview with the patient. This scale may also be helpful in indicating the relevance of improvement. It has been shown to be efficient in demonstrating significant differences in improvement in function from the patients' perspective. Since GAD is associated with considerable impairment of function the SDS may provide a useful comment on the functional relevance of the treatment.[13]

Quality of Life Questionnaire (QOL)

This 16-item patient-rated questionnaire is derived from the Quality of Life, Enjoyment, and Satisfaction Questionnaire. Patients answered questions based on their satisfaction during the previous two weeks regarding mood, health, activities of daily living, and interpersonal relationships on a 5-point scale. Unlike the other efficacy ratings, higher scores on this scale reflect improved function.
(Source: SCT-MD-05 Study Report p. 16)

B.5.6 Outcomes measures and analysis of the non-randomised open label extension study

The efficacy measurements in the non-randomised, open-label extension study are presented in Table B.5.6 below.

Table B.5.6: Outcome measurements in the non-randomised, open-label extension study (SCT-MD-17)

Outcome measurement	Comments
HAM-A	Primary efficacy instrument Subscales also measured – psychic anxiety Anxiety and Tension Items scores reported
CGI	CGI-I measured at each visit CGI-S measured at each visit
HAD	Administered at Week 8, 24 or upon early termination HAD Anxiety Subscale results reported in Section B.6
QOL	Administered at Week 8, 24 or upon early termination
HAMD	Administered at Week 8, 24 or upon early termination
Safety measurements	All adverse events reported

CGI–I = Clinical Global Impression – Improvement, CGI–S = Clinical Global Impression – Severity, HAM-A = Hamilton Anxiety Scale; QOL = Quality of Life Questionnaire

Results of the supportive non-randomised study are presented in Section B.6 (separately from the randomised studies) to provide longer-term data on the continued efficacy and safety of escitalopram in GAD.

Source documents

The source documents with page and/or table references are provided under each table.

B.6 Systematic overview of the results of the direct randomised trials

Summary

Escitalopram provides superior efficacy and similar safety to placebo. This assessment is based on six well designed and conducted direct comparative randomised, controlled studies. The key study outcome (improvement in the HAM-A Total Score) was significantly improved in the escitalopram treatment groups, compared with placebo in all studies, along with a number of important secondary outcomes. s22

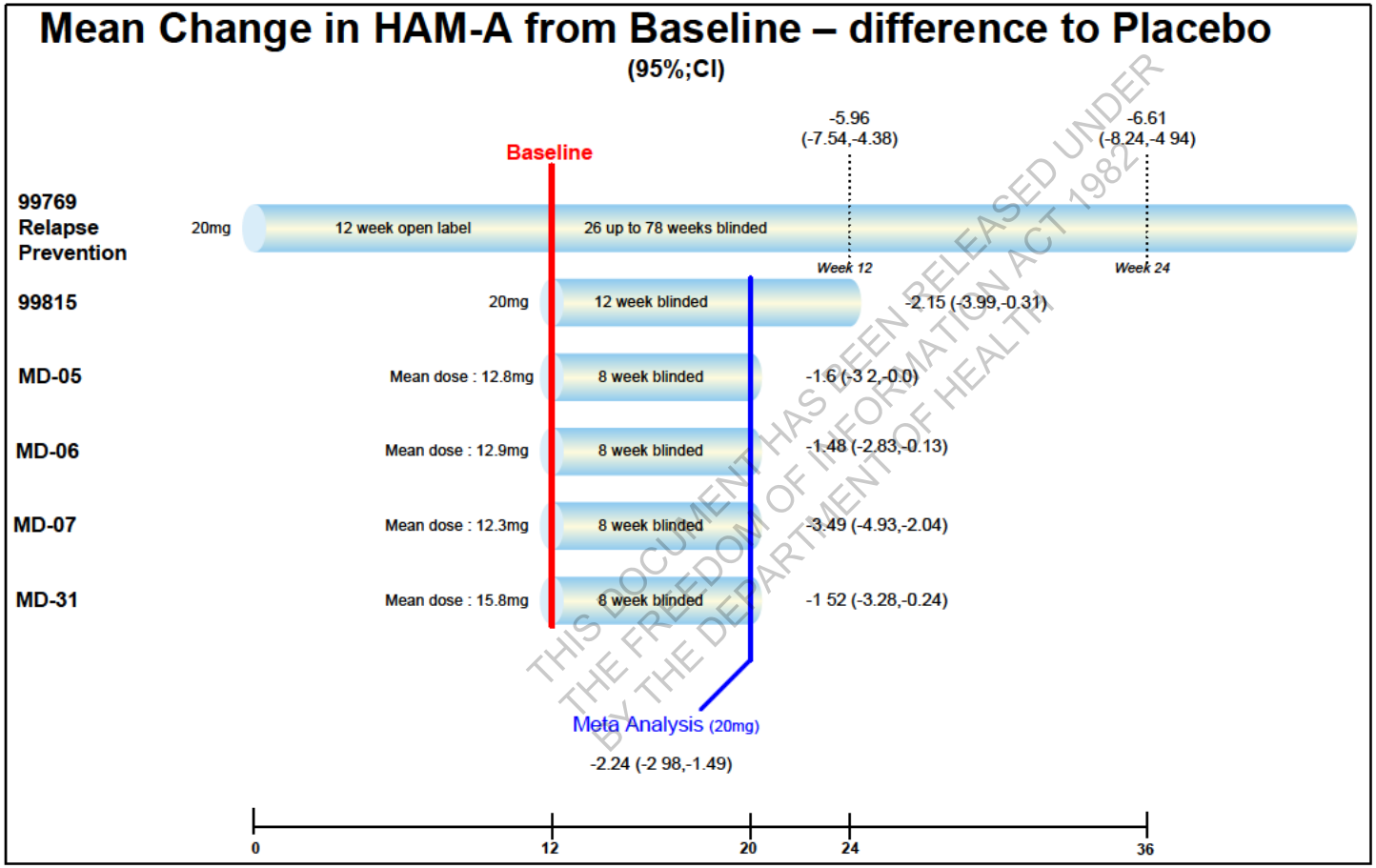
The percentage of patients responding to therapy (based on HAM-A and CGI-I criteria) and achieving remission (based on HAM-A criteria) were also significantly greater with escitalopram, demonstrating the overall superiority of escitalopram therapy across a range of patient-relevant outcomes.

Similar comparative safety was seen with escitalopram and placebo.

The study by Hackett et al.[4] compares the efficacy and safety of benzodiazepines and placebo. The results of this study are presented in order to provide an indirect comparison between escitalopram and benzodiazepine using placebo as a common comparator. There are no significant differences demonstrated between benzodiazepine and placebo in this study.

Figure B.6.2 provides a summary of the timelines and outcomes for the studies presented in this section.

Figure B.6.1: Summary of Clinical Trial Timelines and Primary Outcome



Full details of the results of the included studies are provided in this section and in Attachment 7. The results are presented in the following sub-sections:

B.6.1 Primary outcome result for the randomised, controlled trials – Change in mean HAM-A Total Score

B.6.1.1 Individual Study Results

B.6.1.2 Meta-analysis (Study SCT-MD-05, SCT-MD-06, SCT-MD-07, SCT-MD-31, 99815) at Week 8

B.6.2 Results of the primary outcome for Study 99769 – relapse-prevention study

B.6.3 Results of key secondary efficacy results for the individual studies (provided in full in Attachment 7)

B.6.3.1 escitalopram versus placebo studies

B.6.3.2 placebo vs benzodiazepine studies

B.6.4 Results of the meta-analysis of key secondary efficacy outcomes at Week 8 (provided in full in Attachment 6)

B.6.5 Results of key secondary safety results for the individual studies (provided in full in Attachment 7)

B.6.5.1 escitalopram versus placebo studies

B.6.5.2 placebo vs benzodiazepine studies

B.6.6 Results of the meta-analysis of key secondary safety outcomes at Week 8 (provided in full in Attachment 6)

B.6.7 Results of the supportive study (non-randomised, open-label extension study)

B.6.8 Summary of efficacy and safety data

B.6.8.1 Direct comparison of escitalopram versus placebo (comparator 1)

B.6.8.2 Indirect comparison of escitalopram versus benzodiazepines (comparator 2)

Change in mean HAM-A total score is the primary outcome for Study SCT-MD-05, SCT-MD-06, SCT-MD-07, SCT-MD-31, 99815 (all escitalopram vs placebo) and Hackett et al. (placebo vs benzodiazepine). s47E(d) The primary study outcomes are therefore presented separately first.

This is followed by the primary outcome results of the relapse-prevention study (time to relapse). The results of the meta-analysis of the key secondary outcomes are presented next, including other relevant outcomes based on HAM-A (responders and remitters). Individual study key secondary efficacy and safety results are then presented, with full details available in Attachment 7. Details of the supportive study are also presented.

An overall summary of the efficacy and safety of escitalopram compared with placebo (comparator 1) and escitalopram versus benzodiazepines (comparator 2, made via an indirect comparison using placebo as the common comparator) is then presented.

The results of the key randomised controlled studies demonstrate the efficacy and safety of escitalopram in the treatment of GAD. The results of the relapse prevention study (Study 99269) demonstrate the continued efficacy and safety of escitalopram treatment in patients who have been initially successfully treated with escitalopram.

All study results are sourced from the Clinical Study Reports, with Table and page references provided. Copies of the Clinical Study Reports have been provided with the submission. Information on Hackett et al.[4] is taken from the published paper which is in the Reference Folder provided. The meta-analysis report, including all results is provided in Attachment 6. Some additional supplemental statistical analyses on the individual studies have been performed. These are referred to as “calculated values” in the results tables and are available in Attachment 9.

B.6.1 Primary outcome result for the randomised, controlled trials – Change in mean HAM-A Total Score

The primary outcome in Study SCT-MD-05, SCT-MD-06, SCT-MD-07, SCT-MD-31 and 99815 was mean change in HAM-A Total Score for escitalopram compared with placebo. s47E(d) The results of the study comparing placebo and benzodiazepine (diazepam) is then presented (Hackett et al.[4]). This is followed by the results of the meta-analysis of this outcome for the key randomised controlled studies at Week 12.

B.6.1.1 Individual study results

Study SCT-MD-05, SCT-MD-06, SCT-MD-07 and SCT-MD-31

The results for Study SCT-MD-05, SCT-MD-06, SCT-MD-07 and SCT-MD-31 are presented first in Table B.6.1. These studies were all of 8 weeks duration and had a similar study design, including a flexible escitalopram dose. In all studies the mean change difference in HAM-A total score was significantly greater with escitalopram.

Table B.6.1: Results of primary outcome (Mean change in HAM-A total score, LOCF) – Study SCT-MD-05, SCT-MD-06, SCT-MD-07 and SCT-MD-31

Outcome Timepoint	Trial ID							
	SCT-MD-05		SCT-MD-06		SCT-MD-07		SCT-MD-31	
	Escitalopram[a]	Placebo	Escitalopram[b]	Placebo	Escitalopram[c]	Placebo	Escitalopram[d]	Placebo
n reporting data / N (%)	124 / 128 (96)	128 / 128 (100)	143 / 149 (96)	138 / 145 (95)	154 / 161 (96)	153 / 159 (96)	125 / 131 (95)	135 / 140 (96)
Mean HAM-A total score (SD):								
Baseline	22.8 (3.58)	22.1 (3.71)	22.6 (3.11)	22.6 (3.50)	23.6 (4.63)	23.2 (4.22)	24.21 (3.96)	23.73 (3.24)
Week 8	13.2 (7.54)	14.3 (6.22)	13.4 (6.50)	15.0 (6.13)	12.3 (7.35)	15.7 (6.83)	13.26 (8.18)	14.51 (8.37)
Mean change from baseline (SD) at:								
Week 8	-9.6 (7.14)	-7.7 (6.29)	-9.2 (6.45)	-7.6 (6.04)	-11.3 (7.27)	-7.4 (7.05)	-10.94 (7.44)	-9.21 (7.74)
Difference in mean change (95% CI) - escitalopram versus placebo:								
Week 8	-1.6 (-3.2, -0.0) p = 0.044		-1.48 (-2.83, -0.13) p = 0.032		-3.49 (-4.93, -2.04) p = 0.000		-1.52 (-3.28, 0.24) p = 0.090	

HAM-A = Hamilton Anxiety Scale

a. Flexible dose study, mean escitalopram study dose was 12.8mg daily
b. Flexible dose study, mean escitalopram study dose was 12.9mg daily
c. Flexible dose study, mean escitalopram study dose was 12.3mg daily
d. Flexible dose study, mean escitalopram study dose was 15.8mg daily

Source - Clinical Study Reports:
SCT-MD-05 Table 3.1
SCT-MD-06 Table 3.1
SCT-MD-07 Table 3.1
SCT-MD-31 Table 3.1

Study 99815

The primary outcome results for Study 99815 are presented in Table B.6.2. The results at Week 8 are provided to allow comparison with Study SCT-MD-05, SCT-MD-06, SCT-MD-07 and SCT-MD-31. Week 12, i.e. study endpoint, results are also provided. The patients receiving either dose of escitalopram had significantly improved HAM-A Total Scores at Week 8. By Week 12 the improvement was even greater.

Table B.6.2: Results of primary outcome (Mean change in HAM-A total score, LOCF) – Study 99815

	Escitalopram 10mg	Escitalopram 20mg	Placebo	Source (Study Report)
n reporting data / N (%)	134 / 136 (99)	132 / 133 (99)	138 / 139 (99)	
Mean HAM-A total score (SD):				
Baseline	25.99 (4.14)	27.71 (4.89)	27.12 (4.62)	Table 16
Week 8	11.34 (7.43)	12.82 (8.34)	14.20 (7.42)	
Week 12	9.49 (7.62)	10.95 (8.55)	12.62 (8.39)	
Mean change from baseline (SD) at:				
Week 8	-14.66 (7.61)	-14.89 (8.18)	-12.93 (7.31)	Table 18
Week 12	-16.51 (8.07)	-16.77 (8.99)	-14.51 (7.88)	
Difference in mean change (95% CI) - escitalopram versus placebo:				
Week 8	-2.39 (-4.15, -0.64)	-1.87 (-3.63, -0.12)	-	Table 20
Week 12	-2.56 (-4.40, -0.73)	-2.15 (-3.99, -0.31)	-	

HAM-A = Hamilton Anxiety Scale

Study 99769

While time to relapse was the primary outcome in this study, HAM-A Total Score results were collected as a secondary outcome. The secondary results are presented here with the HAM-A results for the other studies for completeness. Results for Week 12 and 24 (i.e. study endpoint) of the double-blind phase are provided. In addition, the HAM-A Total score at the beginning and end of the open-label phase are presented.

Patients in Study 99769 received 12 weeks of open-label therapy prior to randomisation to escitalopram or placebo. The HAM-A total score at the beginning, Week 8 and end of the open-label phase (Week 12) is presented in Table B.6.3, according to the group that the patient was then randomised into (if they were classified as a responder) or a non-responder group (based on HAM-A>10).

Table B.6.3: HAM-A Total Score and change in the open-label phase, by randomised treatment – Study 99769

	Open label phase responders (patients later randomised to Escitalopram) (n=187)	Open label phase responders (patients later randomised to placebo) (n=188)	Open label phase Non-responders (n=116)	Source (Study Report)
Mean HAM-A total score (SD):				
Beginning of open label phase of study	27.26 (4.15)	27.08 (4.69)	27.72 (4.39)	Table 39
Week 8	8.37 (5.63)	7.67 (4.77)	18.56 (9.09)	
Week 12	5.74 (3.06)	5.07 (3.15)	18.94 (9.24)	
Mean change from beginning of open label phase (SD):				
Week 8	-18.88 (7.16)	-19.41 (6.55)	-9.16 (8.97)	Table 40
Week 12	-21.51 (5.51)	-22.01 (5.69)	-8.78 (9.17)	

HAM-A = Hamilton Anxiety Scale

All patients received 12 weeks of open-label escitalopram therapy prior to study randomisation. Patients who failed to respond to therapy had a similar HAM-A score at initial study entry, but the HAM-A total score only improved to 18.94. These patients then discontinued the study. In contrast the responders to therapy achieved a much greater improvement, with a mean HAM-A score of 5 to 6 after the 12 weeks of open-label escitalopram therapy. They were then randomised to a further minimum of 24 weeks of therapy with either escitalopram or placebo.

The results of the secondary outcome change in mean HAM-A total score is presented in Table B.6.4. Patients in Study 99769 had already received 12 weeks of open-label escitalopram therapy prior to entering the randomised phase of the study. Thus the HAM-A scores were low at baseline. In the escitalopram group the mean values did

not change greatly over the 24 week study, while in the placebo group the values increased (i.e. worsened).

Table B.6.4: Results of secondary outcome (Mean change in HAM-A total score, LOCF) – Study 99769

	Escitalopram	Placebo	Source (Study Report)
n reporting data / N (%)	186 / 187 (99)	187 / 188 (99)	
Mean HAM-A total score (SD):			
Baseline*	5.67 (2.88)	5.02 (3.07)	Table 97
Week 12	7.78 (6.47)	13.10 (8.72)	
Week 24	7.80 (7.31)	13.76 (8.98)	
Mean change from baseline (SD) at:			
Week 12	2.12 (6.54)	8.08 (8.90)	Table 98
Week 24	2.13 (7.46)	8.74 (8.95)	
Difference in mean change# (95% CI) - escitalopram versus placebo:			
Week 12	-5.96 (-7.54 to -4.38; p<0.001)		
Week 24	-6.61 (-8.28 to -4.94; p<0.001)		

HAM-A = Hamilton Anxiety Scale
* Baseline for double-blind phase
# Calculated value, as statistical analyses were not conducted for secondary outcomes

Hackett et al.

The study by Hackett et al.[4] compared the use of placebo with benzodiazepine (diazepam 15 mg/day). The results of this study are used to indirectly compare the efficacy of escitalopram and benzodiazepines (comparator 2) using placebo as a common comparator.

There is very little information provided on the primary efficacy result (Change in HAM-A total score). The available information is provided in Table B.6.5. The publication reports that there was no statistically significant difference between the placebo and benzodiazepine groups.

Table B.6.5: Results of primary outcome (Mean change in HAM-A total score, LOCF) – Hackett et al.

Outcome Timepoint	Benzodiazepine (diazepam 15mg/day)	Placebo	Source of information (publication)
n reporting data / N (%)	89 / NR	97 / NR	
HAM-A Total Score (SD):			
Baseline	28.4 (NR)	27.6 (NR)	p. 184
Week 8	NR	NR	
Adjusted mean change from baseline (SD) at:			
Week 8	-14.8 (NR)	-11.7 (NR)	p. 184
Difference in % patients (95% CI)* versus placebo at:			
Week 8	NR*	-	p. 184

* the difference is reported as being statistically non-significant in the article text (p. 184)

B.6.1.2 Meta-analysis results

The meta-analysis combines the primary outcome results for Study SCT-MD-05, SCT-MD-06, SCT-MD-07, SCT-MD-31 and 99815 at Week 4 and 8. The data is presented below with full details of the study methodology available in Attachment 6. Study 99815 was of 12 weeks duration, while the remainder of the studies were of 8 weeks duration. The 8 week data for all of the studies was meta-analysed. Study 99815 also had two different doses of escitalopram – 10mg daily and 20mg daily. The meta-analysis is performed separately using each of these doses. The results of Study 99769 could not be meta-analysed with the other two studies due to significant differences in study design, leading to differing patient populations.

The results at Week 8 are presented in Figure B.6.2 and Figure B.6.3.

Figure B.6.2: Meta-analysis of primary outcome (mean change in HAM-A total score, LOCF) at Week 8 (escitalopram 10mg dose in Study 99815)

Review: Escitalopram (Lexapro) - GAD
Comparison: 01 Change in HAM-A Total Score (ITT LOCF) - primary endpoint
Outcome: 03 Change in HAM-A Total Score (ITT LOCF) - "Head-to-Head" comparison - final

Study or sub-category	Escitalopram N	Escitalopram Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
SCT-MD-05	124	-9.60(7.14)	128	-7.70(6.29)		19.74	-1.90 [-3.56, -0.24]
SCT-MD-06	143	-9.20(6.45)	138	-7.60(6.04)		25.60	-1.60 [-3.06, -0.14]
SCT-MD-07	154	-11.30(7.27)	153	-7.40(7.05)		21.28	-3.90 [-5.50, -2.30]
SCT-MD-31	125	-10.94(7.44)	135	-9.21(7.74)		16.03	-1.73 [-3.58, 0.12]
Study 99815 (10mg)	134	-14.66(7.61)	138	-12.93(7.31)		17.35	-1.73 [-3.50, 0.04]
Subtotal (95% CI)	680		692			100.00	-2.19 [-2.93, -1.45]
Test for heterogeneity: Chi² = 5.62, df = 4 (P = 0.23), I² = 28.8%							
Test for overall effect: Z = 5.81 (P < 0.00001)							
Total (95% CI)	680		692			100.00	-2.19 [-2.93, -1.45]
Test for heterogeneity: Chi² = 5.62, df = 4 (P = 0.23), I² = 28.8%							
Test for overall effect: Z = 5.81 (P < 0.00001)							

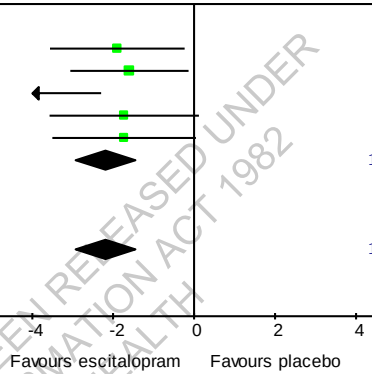
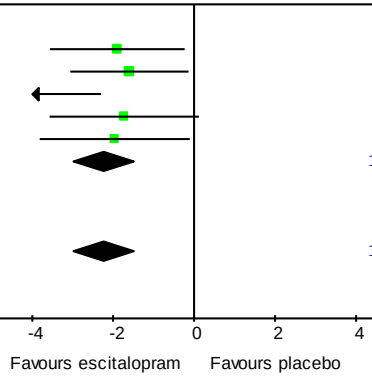


Figure B.6.3: Meta-analysis of primary outcome (mean change in HAM-A total score, LOCF) at Week 8 (escitalopram 20mg dose in Study 99815)

Review: Escitalopram (Lexapro) - GAD
Comparison: 01 Change in HAM-A Total Score (ITT LOCF) - primary endpoint
Outcome: 04 Change in HAM-A Total Score (ITT LOCF) - "Head-to-Head" comparison - final (2)

Study or sub-category	Escitalopram N	Escitalopram Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
SCT-MD-05	124	-9.60(7.14)	128	-7.70(6.29)		20.03	-1.90 [-3.56, -0.24]
SCT-MD-06	143	-9.20(6.45)	138	-7.60(6.04)		25.98	-1.60 [-3.06, -0.14]
SCT-MD-07	154	-11.30(7.27)	153	-7.40(7.05)		21.59	-3.90 [-5.50, -2.30]
SCT-MD-31	125	-10.94(7.44)	135	-9.21(7.74)		16.27	-1.73 [-3.58, 0.12]
Study 99815 (20mg)	132	-14.89(8.18)	138	-12.93(7.31)		16.13	-1.96 [-3.81, -0.11]
Subtotal (95% CI)	678		692			100.00	-2.24 [-2.98, -1.49]
Test for heterogeneity: Chi² = 5.40, df = 4 (P = 0.25), I² = 26.0%							
Test for overall effect: Z = 5.89 (P < 0.00001)							
Total (95% CI)	678		692			100.00	-2.24 [-2.98, -1.49]
Test for heterogeneity: Chi² = 5.40, df = 4 (P = 0.25), I² = 26.0%							
Test for overall effect: Z = 5.89 (P < 0.00001)							



At Week 8 the difference in the weighted mean change was –2.19 (95% CI –2.93, -1.45) pooling the escitalopram 10mg arm in Study 99815 and –2.24 (95% CI –2.98, -1.49) pooling the escitalopram 20mg arm in Study 99815. This is a statistically significant improvement in HAM-A total score in the escitalopram group, compared with placebo.

B.6.2 Results of the primary outcome for Study 99769 – relapse-prevention study

Study 99769 was a relapse prevention study. All patients received 12 weeks of open-label escitalopram, with responders then randomised to receive a minimum of 24 weeks of escitalopram or placebo. The primary study outcome was time to relapse. The results are presented in Table B.6.6 and graphically in Figure B.6.4.

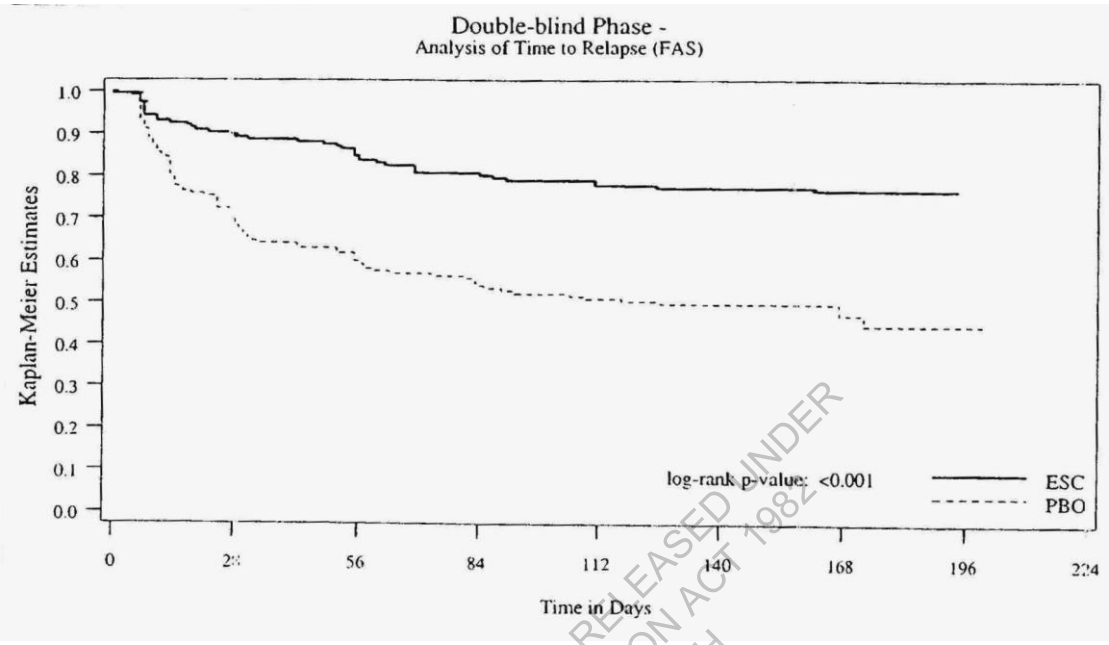
Due to the low number of relapses in the escitalopram group, median survival times could not be estimated satisfactorily. Instead descriptive mean survival times have been presented.

Table B.6.6: Analysis of time to relapse (Study 99769)

Treatment	n / N (%)	No. of relapses	% Relapsed	Mean survival days
Escitalopram Placebo	186 / 187 (99) 187 / 187 (100)	35 105	18.8 56.1	239.4 223.0
Log-rank P value	Hazard Ratio (Cox)	Standard Error	Cox-Model P-value	
1.2.0E-14	4.04	1.22	1.1E-12	

Source – Table 85

Figure B.6.4: Analysis of time to relapse (Study 99269)



The results of the primary analysis show a clear beneficial effect of escitalopram relative to placebo on the time to relapse. (Hazard Ratio 4.04, log rank test, p<0.001). The proportion of patients who relapsed was significantly higher in the placebo group (56%) than in the escitalopram group (19%) (Chi-squared test, p<0.001). This study demonstrates the benefit of escitalopram in reducing the risk of relapse once patients have responded to therapy.

B.6.3 Results of key secondary efficacy outcomes for the individual studies

The key secondary efficacy results are summarised in this section and presented for the individual studies in full in Attachment 7. The studies comparing escitalopram and placebo are presented first (Section B.6.3.1), followed by the single study that compares placebo and benzodiazepines (Hackett et al.[4]) (Section B.6.3.2).

A summary list of the efficacy outcomes and the escitalopram versus placebo studies in which they are available is presented in Table B.6.7 below.

Table B.6.7: Key secondary efficacy results for the individual escitalopram vs placebo studies presented in Section B.6 and Attachment 7

Patient-relevant outcome Escitalopram vs placebo	Trial ID						
	Meta-analysis	SCT-MD-05	SCT-MD-06	SCT-MD-07	SCT-MD-31	99815	99769
Time-point analysed and reported	Week 8	Week 8	Week 8	Week 8	Week 8	Week 8 & 12	Week 12 & 24
Secondary efficacy endpoints							
Change in mean HAM-A response rate (>50% reduction in HAM-A Total Score	√	NR	NR	NR	√	√	NR
Change in mean HAM-A remission rate (HAM-A≤7)	√	NR	NR	NR	√	√	NR
Change in mean HAM-A psychic anxiety subscale score	√	√	√	√	√	√	√
Change in mean HAM-A anxiety item	√	√	√	√	√	√	√
Change in mean HAM-A tension item	√	√	√	√	NR	√	√
Mean CGI-I score	√	√	√	√	√	√	NR
Percentage of patients with CGI-I≤2 (CGI-I responders)	√	√	√	√	√	√	NR
Change in mean CGI-S score	√	√	√	√	√	√	√
Change in mean HAD anxiety subscale score	√	√	√	√	√	√ Week 12	√
Change in mean QOL score	√	√	√	√	√	NR	NR
Change in mean HAMD Total Score	√	√	√	√	√	NR	NR
Secondary safety endpoints							
Total study withdrawals	√	√	√	√	√	√ Week 12	√ at endpoint
Study withdrawals - due to lack of efficacy	√	√	√	√	√	√ Week 12	√ at endpoint
Study withdrawals – due to AEs	√	√	√	√	√	√ Week 12	√ at endpoint
Patients with TEAEs	√	√	√	√	√	√ Week 12	√ at endpoint
TEAEs occurring in ≥5% of patients	√	√	√	√	√	√ Week 12	√ at endpoint

Key: √ = outcome reported in the Study Report or analysed in the meta-analysis and results presented in Section B.6; NA = not available – not a pre-defined study outcome, therefore data not collected; NR = not reported – data not reported for that outcome ; Changes are all change from baseline; AE = adverse events, CGI-I – Clinical Global Impression Improvement, CGI-S– Clinical Global Impression Severity, HAM-A = Hamilton Anxiety Scale, HAD = Hospital anxiety and depression scale, QOL = Quality of Life Questionnaire Score, TEAE = treatment-emergent adverse events
* Reported as a secondary outcome in this study.

The study comparing placebo versus benzodiazepine (Hackett et al.[4]) reports very limited efficacy and safety data. The reported secondary efficacy results are summarised in Table B.6.8.

Table B.6.8: Key secondary efficacy results for the placebo vs benzodiazepines studies presented in Section B.6.3 and in Attachment 7

Patient-relevant outcome Placebo vs benzodiazepine	Trial ID Hackett et al.
Time-point analysed and reported	Week 8
Secondary efficacy endpoints	
Change in mean HAM-A response rate (≥50% reduction in HAM-A Total Score)	√
Percentage of CGI-I responders (patients with CGI-I≤2)	√

B.6.3.1 Summary of key secondary efficacy outcome results for the escitalopram versus placebo studies

The results comparing the relative risk or mean difference between escitalopram and placebo are presented in this section. Full details of the efficacy results are presented in Attachment 7 including baseline values, results for each treatment group at study endpoint, mean change values and differences between treatment groups. With dichotomous data, risk differences, relative risks and number needed to treat (NNT) values, all with 95% confidence intervals, are presented for each outcome in Attachment 7.

Study SCT-MD-05, SCT-MD-06, SCT-MD-07 and SCT-MD-31

The proportion of HAM-A remitters (patients with HAM-A ≤7) and responders (patients with a ≥50% reduction in HAM-A from baseline) was only reported for Study SCT-MD-31 and Study 99815. In Study SCT-MD-31 the proportion of patients that improved was greater with escitalopram than placebo, but this difference was not statistically significant.

The HAM-A Psychic Anxiety Scale total score, HAM-A Anxiety Item score and the HAM-A Tension Item score are all focused on psychic anxiety which is particularly relevant to and disabling in GAD. The improvement in all these scales in all four

studies was statistically significantly greater with escitalopram than placebo. The HAD anxiety scale also focuses on psychic anxiety symptoms. This was also significantly improved in all studies.

The proportion of CGI-I responders (patients with CGI-I≤2) was significantly greater with escitalopram than placebo in Study SCT-MD-06, SCT-MD-07 and SCT-MD-31. The CGI-I score was significantly improved in three of the four studies, while CGI-S was improved in all of the studies.

The results presented in Table B.6.9 are available for Study SCT-MD-31, but not for SCT-MD-05, SCT-MD-06 or SCT-MD-07 as the outcomes weren't reported in these studies. The other key secondary efficacy outcomes are reported in Table B.6.10. Detailed secondary efficacy results are available in Attachment 7.

Table B.6.9: Results of key secondary outcomes (% patients with HAM-A≤7, % patients with ≥50% reduction in HAM-A) – Study SCT-MD-31

Outcome	Escitalopram	Placebo	Source of information (Study Report)
Patients with HAM-A total score ≤7			
n reporting data / N (%)	125 / 131 (95)	135 / 140 (96)	
n (%) patients with HAM-A≤7 at: Week 8	39 (31.2)	32 (23.7)	Table 4.20A
Difference in proportion of patients with HAM-A≤7 vs placebo (95% CI)# at: Week 8	0.07 (-0.03, 0.18)	-	Meta-analysis Report
Relative Risk# (95% CI) vs placebo: Week 8	1.32 (0.88, 1.96)	-	Meta-analysis Report
Patients with ≥50% reduction in HAM-A total score			
n reporting data / N (%)	125 / 131 (95)	135 / 140 (96)	
n (%) patients with ≥50% reduction in HAM-A at: Week 8	66 (52.8)	57 (42.2)	Table 4.18A
Difference in proportion of patients with ≥50% reduction in HAM-A vs placebo (95% CI)# at: Week 8	0.11 (-0.02, 0.23)	-	Meta-analysis Report
Relative Risk# (95% CI) vs placebo: Week 8	1.25 (0.97, 1.62)	-	Meta-analysis Report

HAM-A = Hamilton Anxiety Scale
Calculated value, from meta-analysis
* Calculated value

Table B.6.10: Summary of secondary efficacy results for Study SCT-MD-05, SCT-MD-06, SCT-MD-07 and SCT-MD-31

Outcome Timepoint	Trial ID							
	SCT-MD-05		SCT-MD-06		SCT-MD-07		SCT-MD-31	
	Escitalopram	Placebo	Escitalopram	Placebo	Escitalopram	Placebo	Escitalopram	Placebo
n reporting data / N (%)*	124 / 128 (96)	128 / 128 (100)	143 / 149 (96)	138 / 145 (95)	154 / 161 (96)	153 / 159 (96)	125 / 131 (95)	135 / 140 (96)
HAM-A Psychic Anxiety Subscale:								
Difference in mean change (95% CI) - escitalopram versus placebo:								
Week 8	-1.3 (-2.3, -0.3)		-1.43 (-2.30, -0.57)		-2.35 (-3.23, -1.47)		-1.22 (-2.25, -0.18)	
HAM-A Anxiety Item:								
Difference in mean change (95% CI) - escitalopram versus placebo:								
Week 8	-0.2 (-0.4, 0.0)		-0.36 (-0.56, -0.17)		-0.52 (-0.71, -0.33)		-0.29 (-0.51, -0.06)	
HAM-A Tension Item:								
Difference in mean change (95% CI) - escitalopram versus placebo:								
Week 8	-0.2 (-0.5, -0.0)		-0.31 (-0.51, -0.10)		-0.38 (-0.58, -0.18)		NR	
Clinical Global Impression – Improvement*:								
Difference in mean change (95% CI) - escitalopram versus placebo:								
Week 8	-0.2 (-0.5, 0.1)		-0.25 (-0.49, -0.02)		-0.46 (-0.69, -0.23)		-0.43 (-0.71, -0.15)	
Patients with CGI≤2:								
Difference# (using proportions) in mean change (95% CI) - escitalopram versus placebo:								
Week 8	0.08 (-0.04, 0.20)		0.15 (0.04, 0.26)		0.20 (0.09, 0.31)		0.14 (0.02, 0.26)	
Relative Risk# (95% CI) - escitalopram versus placebo at:								
Week 8	1.19 (0.90, 1.56)		1.45 (1.08, 1.94)		1.52 (1.19, 1.95)		1.31 (1.04, 1.65)	
Clinical Global Impression – Severity:								
Difference in mean change (95% CI) - escitalopram versus placebo:								
Week 8	-0.3 (-0.5, -0.0)		-0.31 (-0.53, -0.08)		-0.47 (-0.70, -0.25)		-0.33 (-0.60, -0.05)	

Table B.6.10: Summary of secondary efficacy results for Study SCT-MD-05, SCT-MD-06, SCT-MD-07 and SCT-MD-31 (continued)

Outcome Timepoint	Trial ID							
	SCT-MD-05		SCT-MD-06		SCT-MD-07		SCT-MD-31	
	Escitalopram	Placebo	Escitalopram	Placebo	Escitalopram	Placebo	Escitalopram	Placebo
HAD Anxiety Subscale Score:								
Difference in mean change (95% CI) - escitalopram versus placebo:								
Week 8	-1.5 (-2.6, -0.4)		-1.15 (-2.00, -0.30)		-2.50 (-3.37, -1.63)		-1.10 (-2.11, -0.10)	
QOL Score:								
Difference in mean change (95% CI) - escitalopram versus placebo:								
Week 8	2.5 (0.3, 4.8)		2.18 (0.12, 4.24)		5.90 (3.79, 8.00)		1.52 (-0.91, 3.94)	

CGI-I = Clinical Global Impression – Improvement, HAM-A = Hamilton Anxiety Scale, QOL = Quality of Life Questionnaire, HAD = Hospital Anxiety and Depression Scale
* for most outcomes, see tables in Attachment 7 for precise details of each study

Study 99815

Table B.6.11 presents the results for HAM-A remitters (patients with HAM-A ≤7/ patients with HAM-A≤9) and responders (Patients with HAM-A reduction ≥50% compared with baseline) at Week 8 and Week 12 (study endpoint). There were significantly more HAM-A remitters with escitalopram therapy compared with placebo at Study endpoint. There were also more HAM-A responders, though the difference was not statistically significant.

Table B.6.11: Summary of secondary outcomes for Study 99815 (HAM-A remitters and responders)

Outcome	Escitalopram 10mg	Escitalopram 20mg	Placebo
n reporting data / N (%)	134 / 136 (99)	132 / 133 (99)	138 / 139 (99)
Patients with HAM-A total score ≤7 (HAM-A remitters)			
Difference in % patients with HAM-A≤7 vs placebo (95% CI) at:			
Week 8	12.6 (2.0, 23.2)	10.8 (0.3, 21.4)	
Week 12	18.1 (6.7, 29.4)	13.5 (2.1, 24.9)	-
Relative Risk# (95% CI) vs placebo:			
Week 8	1.58 (1.07, 2.34)	1.50 (1.00, 2.24)	
Week 12	1.61 (1.18, 2.20)	1.45 (1.05, 2.01)	
Patients with HAM-A total score ≤9 (HAM-A remitters, alternative definition)			
Relative Risk* (95% CI) vs placebo:			
Week 8	1.53 (1.13, 2.08)	1.22 (0.87, 1.69)	-
Week 12	1.29 (1.01, 1.64)	1.29 (1.01, 1.64)	-
NNT* (95% CI) vs placebo			
Week 8	6 (4, 20)	15 (6, 22)	-
Week 12	8 (4, 143)	8 (4, 99)	-
Patients with ≥50% reduction in HAM-A Total Score (HAM-A responders)			
Difference in % patients with ≥50% reduction in HAM-A vs placebo (95% CI) at:			
Week 8	10.5 (-1.3, 22.2)	7.6 (-4.2, 19.5)	
Week 12	10.0 (-1.1, 21.2)	8.9 (-2.4, 20.1)	-
Relative Risk* (95% CI) vs placebo:			
Week 8	1.21 (0.98, 1.49)	1.15 (0.92, 1.43)	
Week 12	1.16 (0.98, 1.38)	1.14 (0.96, 1.36)	

HAM-A = Hamilton Anxiety Scale
* calculated value

Other secondary efficacy outcomes for Study 99815 are presented in Table B.6.12. Patients continued to improve between Week 8 and Week 12 of escitalopram therapy. With all outcomes patients receiving escitalopram had a improved outcome compared with placebo. With HAM-A Tension score, CGI-I, patients with CGI-I $\leq$2, CGI-S total score and the HAD Anxiety subscale these improvements were statistically significantly greater at study endpoint (Week 12).

Table B.6.12: Summary of secondary efficacy outcomes for Study 99815 (HAM-A subscales/items, CGI-I, CGI-S, HAD Anxiety Scale)

Outcome Timepoint	Escitalopram 10mg	Escitalopram 20mg	Placebo
n reporting data / N (%)	134 / 136 (99)	132 / 133 (99)	138 / 139 (99)
HAM-A Psychic Anxiety Subscale Score:			
Difference in mean change* (95% CI) - escitalopram versus placebo:			
Week 8	-1.76 (-2.79, -0.73)	-0.95 (-1.98, 0.08)	-
Week 12	-1.63 (-2.69, -0.57)	-1.04 (-2.11, 0.03)	-
HAM-A Anxiety# Item Score:			
Difference in mean change* (95% CI) - escitalopram versus placebo:			
Week 8	-0.32 (-0.54, -0.10)	-0.14 (-0.36, 0.08)	-
Week 12	-0.37 (-0.59, -0.14)	-0.18 (-0.40, 0.05)	-
HAM-A Tension Item Score:			
Difference in mean change* (95% CI) - escitalopram versus placebo:			
Week 8	-0.33 (-0.55, -0.12)	-0.11 (-0.33, 0.10)	-
Week 12	-0.27 (-0.50, -0.04)	-0.15 (-0.38, 0.07)	-
Clinical Global Impression – Improvement (CGI-I) Total Score#:			
Difference in mean change* (95% CI) - escitalopram versus placebo:			
Week 8	-0.38 (-0.63, -0.13)	-0.26 (-0.51, -0.01)	-
Week 12	-0.40 (-0.67, -0.14)	-0.27 (-0.53, -0.00)	-
Patients with CGI-I≤2:			
Difference in % patients (95% CI) with CGI-I≤2 versus placebo at:			
Week 8	15.1 (3.9, 26.3)	10.2 (-1.3, 21.7)	-
Week 12	15.3 (4.7, 26.0)	11.2 (0.2, 22.2)	-
Relative Risk (95% CI) versus placebo:			
Week 8	1.26 (1.06, 1.51)	1.18 (0.98, 1.42)	
Week 12	1.24 (1.06, 1.45)	1.18 (1.00, 1.39)	
Clinical Global Impression – Severity (CGI-S) Score:			
Difference in mean change* (95% CI) - escitalopram versus placebo:			
Week 8	-0.51 (-0.78, -0.25)	-0.33 (-0.60, -0.06)	-
Week 12	-0.50 (-0.78, -0.21)	-0.34 (-0.62, -0.05)	-
HAD Anxiety Subscale Score:			
Difference in mean change* (95% CI) - escitalopram versus placebo:			
Week 12	-1.69 (-2.69, -0.69)	-1.59 (-2.61, -0.57)	-

CGI-I = Clinical Global Impression – Improvement, CGI-S = Clinical Global Impression – Severity, HAD = Hospital Anxiety and Depression Scale, HAM-A = Hamilton Anxiety Scale
* analysed using ANCOVA

Study 99769

The secondary outcome results for the relapse prevention Study 99769 are summarised in Table B.6.13 below. Full results are available in Attachment 7. All secondary outcomes were significantly improved with escitalopram, compared with placebo, demonstrating a consistent, positive overall effect of escitalopram on GAD. A number of these outcomes focussed on psychic anxiety that is particularly prominent in and disabling for patients with GAD.

Table B.6.13: Summary of secondary efficacy outcomes for Study 99769

Outcome Timepoint	Escitalopram	Placebo
n reporting data / N (%)	186 / 187 (99)	187 / 188 (99)
HAM-A Psychic Anxiety Subscale Score:		
Difference in mean change* (95% CI) – escitalopram versus placebo:		
Week 12	-3.69 (-4.64 to -2.74, p<0.001)	
Week 24	-3.91 (-4.91 to -2.91, p<0.001)	
HAM-A Anxiety# Item Score:		
Difference in mean change (95% CI) – escitalopram versus placebo:		
Week 12	-0.8 (-1.01 to -0.59, p<0.001)	
Week 24	-0.81 (-1.03 to -0.59, p<0.001)	
HAM-A Tension Item Score:		
Difference in mean change (95% CI) – escitalopram versus placebo:		
Week 12	-0.8 (-1.02 to -0.58, p<0.001)	
Week 24	-0.81 (-1.04 to -0.58, p<0.001)	
Clinical Global Impression – Severity (CGI-S) Score:		
Difference in mean change* (95% CI) – escitalopram versus placebo:		
Week 12	-1.03 (-1.29 to -0.77, p<0.001)	
Week 24	-1.19 (-1.46 to -0.92, p<0.001)	
HAD Anxiety Score:		
Difference in mean change (95% CI) – escitalopram versus placebo:		
Week 12	-2.82 (-3.68 to -1.96, p<0.001)	
Week 24	-3.07 (-4.00 to -2.14, p<0.001)	

HAD = Hospital Anxiety and Depression Scale, HAM-A = Hamilton Anxiety Scale

B.6.3.2 Summary of key secondary efficacy outcome results for the placebo versus benzodiazepine study (Hackett et al.)

The results for Hackett et al.[4] are from the published paper. Very little data is presented on the overall study results that compare placebo with benzodiazepines (diazepam), as most of the results section reports the sub-group analyses based on placebo response rates.

For the outcomes reported there are no significant differences between placebo and benzodiazepine (diazepam) (Table B.6.14).

Table B.6.14: Secondary efficacy results for Hackett et al.

Outcome Timepoint	Benzodiazepine (diazepam 15mg/day) vs placebo
Patients with ≥50% reduction in HAM-A Total Score:	
Difference in % patients (95% CI)* versus placebo at:	
Week 8	11 (-3.5, 25.1)
Relative Risk (95% CI)* versus placebo:	
Week 8	1.24 (0.93, 1.65)
Patients with Clinical Global Impression – Improvement (CGI-I) ≤2:	
n (%) patients:	
Difference in % patients (95% CI)* versus placebo at:	
Week 8	12.7 (-0.3, 25.4)
Relative Risk (95% CI)* versus placebo:	
Week 8	1.19 (0.996, 1.426)

* calculated values
HAM-A - Hamilton Anxiety Scale
n=89 for benzodiazepine and n=97 for placebo

B.6.4 Results of the meta-analysis of key secondary efficacy outcomes

Revman format results for the meta-analysis of the key secondary outcomes of the treatment studies (Study 99270 and 99012) are presented in Figure B.6.5to Figure B.6.21 below. The full meta-analysis report is provided in Attachment 6. Results are presented at 8 weeks. Each outcome is presented twice with continuous outcomes – using the escitalopram 10mg arm in Study 99815 and then separately using the

escitalopram 20mg arm. Most of the outcomes were reported in all of the studies, though there were some outcomes reported in only some of the studies. The studies included in each outcome of the meta-analysis are clearly reported in each of the figures.

It is important to note that Study 99815 was of 12 weeks duration, so the meta-analysed results do not reflect the value of escitalopram during the final third of study treatment. Due to the differences in study design with Study 99815 (i.e. the fixed escitalopram doses and duration of 12 weeks) the meta-analyses were conducted with and without this study included. No significant differences were seen when the study was or wasn't included, so the meta-analysis results including Study 99815 are presented in this section. The results without Study 99815 are available in the Meta-analysis Report in Attachment 6.

In addition, due to differences in study design the relapse-prevention study (Study 99769) could not be validly meta-analysed with the other two treatment studies. Study 99769 provides data on the use of escitalopram for at least 24 weeks, rather than the 8 weeks reported in the meta-analysis.

Summary of meta-analysis results

Therapy with escitalopram significantly improved outcomes in all key secondary efficacy outcomes reported in the meta-analysis at 8 weeks, compared with placebo.

The percentage of HAM-A remitters (HAM-A≤7) was significantly reduced after 8 weeks therapy with escitalopram compared with placebo (RR 1.44, 95% CI 1.10-1.87). A HAM-A remitter is effectively 'cured' of GAD, with a HAM-A score reflecting a non-affected person, and is thus a very high hurdle to achieve. HAM-A responders (percentage of patients with ≥50% improvement in HAM-A total score) was also significantly greater with escitalopram compared with placebo (RR 1.20, 95% CI 1.03, 1.40). Significant improvements in the HAM-A Psychic Anxiety Subscale and Anxiety and Tension Items were also reported– a 1.70 unit greater improvement (RR –1.70, 95% CI: -2.14 to -1.26, p<0.001), a 0.34 unit improvement (RR 0.34, 95% CI: -0.44 to -0.24, p<0.001) and a 0.31 unit improvement (RR –0.31, 95% CI: -0.42 to -0.19, p<0.001), respectively (including the escitalopram 10mg arm

in Study 99815). These subscales and items all measure aspects of the psychic anxiety that causes significant impairment in patients with GAD, and thus particularly demonstrate the efficacy of escitalopram in improving GAD. Changes in continuous variables with respect to HAM-A Psychic Anxiety Subscale, HAM-A Anxiety Item and HAM-A Tension Item were also statistically significant in favour of escitalopram compared to placebo at the time-point of 8 weeks

Patient results based on the Clinical Global Impression – Improvement and – Severity scales demonstrate significant responses to escitalopram therapy. The percentage of patients with CGI-I scores ≤2 (i.e. patients that were very much or much improved) was 31% greater with escitalopram (RR 1.31, 95% CI 1.18, 1.45). HAD Anxiety scores and Quality of Life scale measurements also significantly improved with escitalopram.

The HAMD score was not an efficacy endpoint, but rather an assessment of depressive status. While escitalopram was superior to placebo at week 8, the HAMD score seen throughout the studies in all treatment groups at Week 8 ranged from 8.4 to a maximum of 10.8. A HAMD score of 10-13 indicates mild depression, with lower scores indicating the absence of depression (source: http://www.cipralex.com/for_your_patients/). Thus all patients were below the recognised cut-off for a depressive episode at Study entry and endpoint (i.e. below a HAMD score of 17 which would indicate moderate to severe depression). Thus the benefit seen with escitalopram therapy in the Studies was due to treatment of GAD, rather than co-morbid depression.

Hamilton Anxiety Scale (HAM-A) – responders, remitters and sub-scale/item results

The results are presented in Figure B.6.5 to Figure B.6.12.

Figure B.6.5: Number and Percentage of Patients with HAM-A ≤7 (ITT LOCF)

Review: Escitalopram (Lexapro) - GAD
Comparison: 08 Number of Patients with HAM-A<=7 (ITT LOCF) - secondary endpoint
Outcome: 01 Number of Patients with HAM-A<=7 (ITT LOCF) - final

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-31	39/125	32/135		44.72	1.32 [0.88, 1.96]
Study 99815 (all)	89/266	30/138		55.28	1.54 [1.07, 2.20]
Total (95% CI)	391	273		100.00	1.44 [1.10, 1.87]

Total events: 128 (Escitalopram), 62 (Placebo)
Test for heterogeneity: Chi² = 0.33, df = 1 (P = 0.57), I² = 0%
Test for overall effect: Z = 2.65 (P = 0.008)

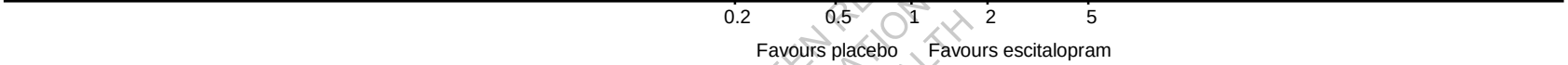


Figure B.6.6: Number and Percentage of Patients with ≥50% reduction in HAM-A Total Score (ITT LOCF)

Review: Escitalopram (Lexapro) - GAD
Comparison: 07 Number of Patients with =>50% reduction in HAM-A Total Score (ITT LOCF) - secondary endpoint
Outcome: 01 Number of Patients with =>50% reduction in HAM-A Total Score (ITT LOCF) - 8 weeks

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-31	66/125	57/135		35.63	1.25 [0.97, 1.62]
Study 99815 (all)	159/266	70/138		64.37	1.18 [0.97, 1.43]
Total (95% CI)	391	273		100.00	1.20 [1.03, 1.40]

Total events: 225 (Escitalopram), 127 (Placebo)
Test for heterogeneity: Chi² = 0.13, df = 1 (P = 0.72), I² = 0%
Test for overall effect: Z = 2.36 (P = 0.02)

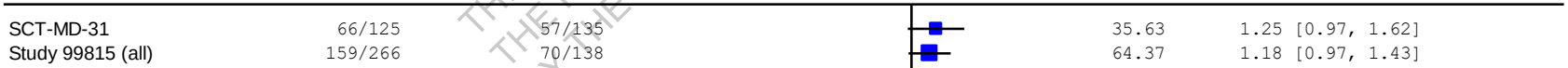


Figure B.6.7: Change in HAM-A Psychic Anxiety Subscale (ITT LOCF, Study 99815 escitalopram 10mg arm included)

Review: Escitalopram (Lexapro) - GAD
Comparison: 12 Change in HAM-A Psychic Anxiety Subscale (ITT LOCF) - secondary endpoint
Outcome: 02 Change in HAM-A Psychic Anxiety Subscale (ITT LOCF) - "Head-to-Head" comparison - final

Study or sub-category	Escitalopram N	Escitalopram Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
SCT-MD-05	124	-5.30(4.16)	128	-4.00(3.76)		20.31	-1.30 [-2.28, -0.32]
SCT-MD-06	143	-5.50(3.86)	138	-3.90(3.80)		24.32	-1.60 [-2.50, -0.70]
SCT-MD-07	154	-6.40(4.05)	153	-3.80(4.30)		22.34	-2.60 [-3.53, -1.67]
SCT-MD-31	125	-6.27(4.45)	135	-4.84(4.57)		16.22	-1.43 [-2.53, -0.33]
Study 99815 (10mg)	134	-7.81(4.85)	138	-6.40(4.18)		16.81	-1.41 [-2.49, -0.33]
Subtotal (95% CI)	680		692			100.00	-1.70 [-2.14, -1.26]
Test for heterogeneity: Chi² = 4.76, df = 4 (P = 0.31), I² = 16.0%							
Test for overall effect: Z = 7.56 (P < 0.00001)							
Total (95% CI)	680		692			100.00	-1.70 [-2.14, -1.26]
Test for heterogeneity: Chi² = 4.76, df = 4 (P = 0.31), I² = 16.0%							
Test for overall effect: Z = 7.56 (P < 0.00001)							

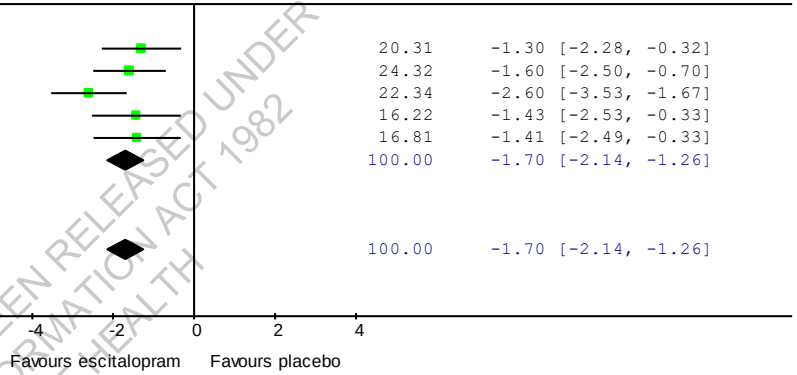


Figure B.6.8: Change in HAM-A Psychic Anxiety Subscale (ITT LOCF, Study 99815 escitalopram 20mg arm included)

Review: Escitalopram (Lexapro) - GAD
Comparison: 12 Change in HAM-A Psychic Anxiety Subscale (ITT LOCF) - secondary endpoint
Outcome: 03 Change in HAM-A Psychic Anxiety Subscale (ITT LOCF) - "Head-to-Head" comparison - final (2)

Study or sub-category	Escitalopram N	Escitalopram Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
SCT-MD-05	124	-5.30(4.16)	128	-4.00(3.76)		19.94	-1.30 [-2.28, -0.32]
SCT-MD-06	143	-5.50(3.86)	138	-3.90(3.80)		23.87	-1.60 [-2.50, -0.70]
SCT-MD-07	154	-6.40(4.05)	153	-3.80(4.30)		21.93	-2.60 [-3.53, -1.67]
SCT-MD-31	125	-6.27(4.45)	135	-4.84(4.57)		15.92	-1.43 [-2.53, -0.33]
Study 99815 (20mg)	132	-7.36(4.38)	138	-6.40(4.18)		18.33	-0.96 [-1.98, 0.06]
Subtotal (95% CI)	678		692			100.00	-1.62 [-2.05, -1.18]
Test for heterogeneity: Chi² = 6.35, df = 4 (P = 0.17), I² = 37.0%							
Test for overall effect: Z = 7.23 (P < 0.00001)							
Total (95% CI)	678		692			100.00	-1.62 [-2.05, -1.18]
Test for heterogeneity: Chi² = 6.35, df = 4 (P = 0.17), I² = 37.0%							
Test for overall effect: Z = 7.23 (P < 0.00001)							

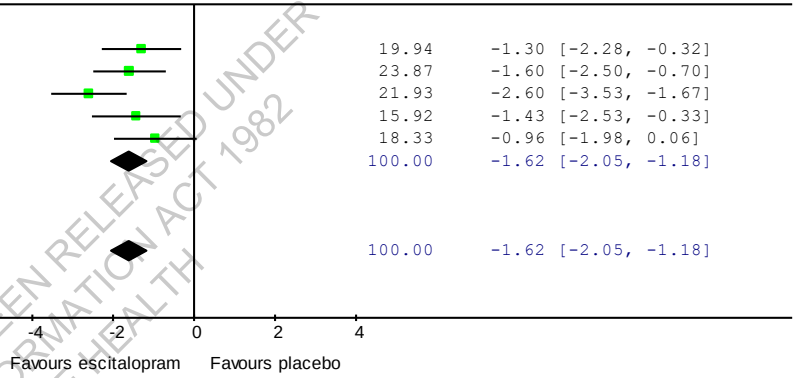


Figure B.6.9: Change in HAM-A Anxiety Item (ITT LOCF, Study 99815 escitalopram 10mg arm included)

Review: Escitalopram (Lexapro) - GAD
Comparison: 13 Change in HAM-A Anxiety Item (ITT LOCF) - secondary endpoint
Outcome: 02 Change in HAM-A Anxiety Item (ITT LOCF) - "Head-to-Head" comparison - final

Study or sub-category	Escitalopram N	Escitalopram Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
SCT-MD-05	124	-1.00(0.95)	128	-0.80(0.86)		20.25	-0.20 [-0.42, 0.02]
SCT-MD-06	143	-1.20(0.87)	138	-0.80(0.92)		23.13	-0.40 [-0.61, -0.19]
SCT-MD-07	154	-1.20(0.95)	153	-0.70(0.97)		22.01	-0.50 [-0.71, -0.29]
SCT-MD-31	125	-1.23(1.05)	135	-0.92(0.99)		16.44	-0.31 [-0.56, -0.06]
Study 99815 (10mg)	134	-1.51(1.07)	138	-1.26(0.91)		18.17	-0.25 [-0.49, -0.01]
Subtotal (95% CI)	680		692			100.00	-0.34 [-0.44, -0.24]
Test for heterogeneity: Chi² = 4.56, df = 4 (P = 0.34), I² = 12.3%							
Test for overall effect: Z = 6.60 (P < 0.00001)							
Total (95% CI)	680		692			100.00	-0.34 [-0.44, -0.24]
Test for heterogeneity: Chi² = 4.56, df = 4 (P = 0.34), I² = 12.3%							
Test for overall effect: Z = 6.60 (P < 0.00001)							

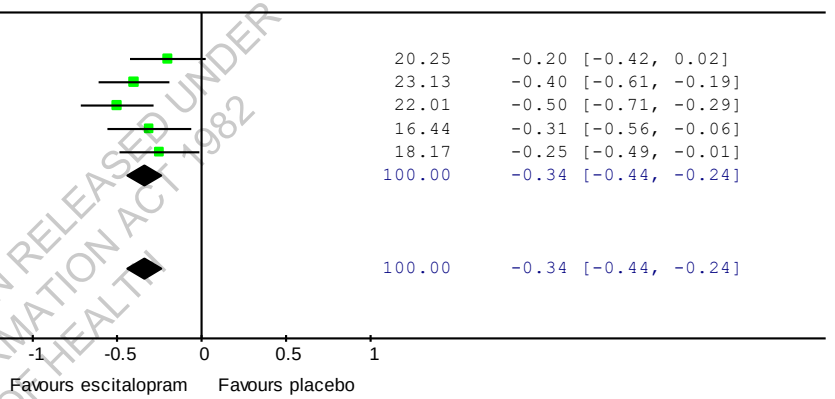


Figure B.6.10: Change in HAM-A Anxiety Item (ITT LOCF, Study 99815 escitalopram 20mg arm included)

Review: Escitalopram (Lexapro) - GAD
Comparison: 13 Change in HAM-A Anxiety tem (ITT LOCF) - secondary endpoint
Outcome: 03 Change in HAM-A Anxiety tem (ITT LOCF) - "Head-to-Head" comparison - final (2)

Study or sub-category	Escitalopram N	Escitalopram Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
SCT-MD-05	124	-1.00(0.95)	128	-0.80(0.86)		20.07	-0.20 [-0.42, 0.02]
SCT-MD-06	143	-1.20(0.87)	138	-0.80(0.92)		22.93	-0.40 [-0.61, -0.19]
SCT-MD-07	154	-1.20(0.95)	153	-0.70(0.97)		21.82	-0.50 [-0.71, -0.29]
SCT-MD-31	125	-1.23(1.05)	135	-0.92(0.99)		16.30	-0.31 [-0.56, -0.06]
Study 99815 (20mg)	132	-1.36(1.02)	138	-1.26(0.91)		18.88	-0.10 [-0.33, 0.13]
Subtotal (95% CI)	678		692			100.00	-0.31 [-0.41, -0.21]
Test for heterogeneity: Chi² = 7.82, df = 4 (P = 0.10), I² = 48.8%							
Test for overall effect: Z = 6.06 (P < 0.00001)							
Total (95% CI)	678		692			100.00	-0.31 [-0.41, -0.21]
Test for heterogeneity: Chi² = 7.82, df = 4 (P = 0.10), I² = 48.8%							
Test for overall effect: Z = 6.06 (P < 0.00001)							

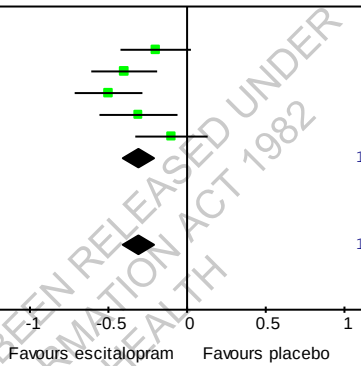


Figure B.6.11: Change in HAM-A Tension Item (ITT LOCF, Study 99815 escitalopram 10mg arm included)

Review: Escitalopram (Lexapro) - GAD
Comparison: 14 Change in HAM-A Tension Item (ITT LOCF) - secondary endpoint
Outcome: 02 Change in HAM-A Tension Item (ITT LOCF) - "Head-to-Head" comparison - final

Study or sub-category	Escitalopram N	Escitalopram Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
SCT-MD-05	124	-0.90(1.02)	128	-0.70(0.89)		23.06	-0.20 [-0.44, 0.04]
SCT-MD-06	143	-1.10(0.92)	138	-0.70(0.97)		26.39	-0.40 [-0.62, -0.18]
SCT-MD-07	154	-1.20(1.00)	153	-0.80(1.00)		25.80	-0.40 [-0.62, -0.18]
Study 99815 (10mg)	134	-1.63(0.99)	138	-1.42(0.93)		24.75	-0.21 [-0.44, 0.02]
Subtotal (95% CI)	555		557			100.00	-0.31 [-0.42, -0.19]
Test for heterogeneity: Chi² = 2.82, df = 3 (P = 0.42), I² = 0%							
Test for overall effect: Z = 5.29 (P < 0 00001)							
Total (95% CI)	555		557			100.00	-0.31 [-0.42, -0.19]
Test for heterogeneity: Chi² = 2.82, df = 3 (P = 0.42), I² = 0%							
Test for overall effect: Z = 5.29 (P < 0 00001)							

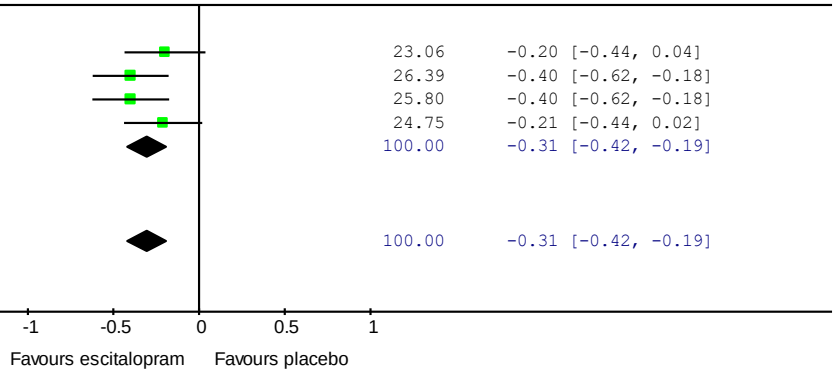
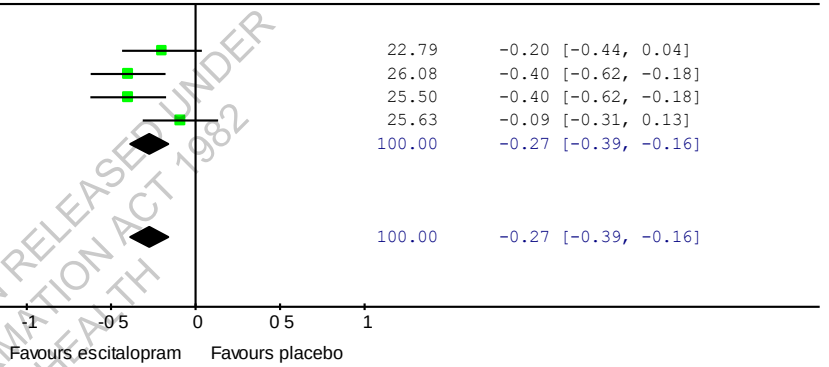


Figure B.6.12: Change in HAM-A Tension Item (ITT LOCF, Study 99815 escitalopram 20mg arm included)

Review: Escitalopram (Lexapro) - GAD
Comparison: 14 Change in HAM-A Tension Item (ITT LOCF) - secondary endpoint
Outcome: 03 Change in HAM-A Tension Item (ITT LOCF) - "Head-to-Head" comparison - final (2)

Study or sub-category	Escitalopram N	Escitalopram Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
SCT-MD-05	124	-0.90(1.02)	128	-0.70(0.89)		22.79	-0.20 [-0.44, 0.04]
SCT-MD-06	143	-1.10(0.92)	138	-0.70(0.97)		26.08	-0.40 [-0.62, -0.18]
SCT-MD-07	154	-1.20(1.00)	153	-0.80(1.00)		25.50	-0.40 [-0.62, -0.18]
Study 99815 (20mg)	132	-1.51(0.94)	138	-1.42(0.93)		25.63	-0.09 [-0.31, 0.13]
Subtotal (95% CI)	553		557			100.00	-0.27 [-0.39, -0.16]
Test for heterogeneity: Chi² = 5.45, df = 3 (P = 0.14), I² = 45.0%							
Test for overall effect: Z = 4.77 (P < 0.00001)							
Total (95% CI)	553		557			100.00	-0.27 [-0.39, -0.16]
Test for heterogeneity: Chi² = 5.45, df = 3 (P = 0.14), I² = 45.0%							
Test for overall effect: Z = 4.77 (P < 0.00001)							



Clinical Global Impression – Improvement (CGI-I)

The results are presented in Figure B.6.13 to Figure B.6.15.

Figure B.6.13: CGI Improvement (ITT LOCF, Study 99815 escitalopram 10mg arm included)

Review: Escitalopram (Lexapro) - GAD
Comparison: 02 CGI Improvement (ITT LOCF) - a change characteristic - secondary endpoint
Outcome: 02 CGI Improvement (ITT LOCF) - "Head-to-Head" comparison - final

Study or sub-category	Escitalopram N	Escitalopram Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
SCT-MD-05	124	2.60(1.16)	128	2.80(0.99)		18.74	-0.20 [-0.47, 0.07]
SCT-MD-06	143	2.60(1.00)	138	2.80(1.04)		23.39	-0.20 [-0.44, 0.04]
SCT-MD-07	154	2.40(1.09)	153	2.80(1.09)		22.41	-0.40 [-0.64, -0.16]
SCT-MD-31	125	2.29(1.16)	135	2.68(1.26)		15.40	-0.39 [-0.68, -0.10]
Study 99815 (10mg)	134	2.08(1.16)	138	2.41(1.00)		20.06	-0.33 [-0.59, -0.07]
Subtotal (95% CI)	680		692			100.00	-0.30 [-0.42, -0.18]
Test for heterogeneity: Chi² = 2.27, df = 4 (P = 0.69), I² = 0%							
Test for overall effect: Z = 5.10 (P < 0.00001)							
Total (95% CI)	680		692			100.00	-0.30 [-0.42, -0.18]
Test for heterogeneity: Chi² = 2.27, df = 4 (P = 0.69), I² = 0%							
Test for overall effect: Z = 5.10 (P < 0.00001)							

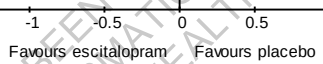


Figure B.6.14: CGI Improvement (ITT LOCF, Study 99815 escitalopram 20mg arm included)

Review: Escitalopram (Lexapro) - GAD
Comparison: 02 CGI Improvement (ITT LOCF) - a change characteristic - secondary endpoint
Outcome: 03 CGI Improvement (ITT LOCF) - "Head-to-Head" comparison - final (2)

Study or sub-category	Escitalopram N	Escitalopram Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
SCT-MD-05	124	2.60(1.16)	128	2.80(0.99)		18.62	-0.20 [-0.47, 0.07]
SCT-MD-06	143	2.60(1.00)	138	2.80(1.04)		23.24	-0.20 [-0.44, 0.04]
SCT-MD-07	154	2.40(1.09)	153	2.80(1.09)		22.26	-0.40 [-0.64, -0.16]
SCT-MD-31	125	2.29(1.16)	135	2.68(1.26)		15.30	-0.39 [-0.68, -0.10]
Study 99815 (20mg)	132	2.17(1.12)	138	2.41(1.00)		20.58	-0.24 [-0.49, 0.01]
Subtotal (95% CI)	678		692			100.00	-0.28 [-0.40, -0.17]
Test for heterogeneity: Chi² = 2.34, df = 4 (P = 0.67), I² = 0%							
Test for overall effect: Z = 4.80 (P < 0.00001)							
Total (95% CI)	678		692			100.00	-0.28 [-0.40, -0.17]
Test for heterogeneity: Chi² = 2.34, df = 4 (P = 0.67), I² = 0%							
Test for overall effect: Z = 4.80 (P < 0.00001)							

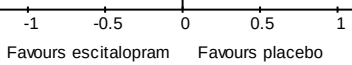
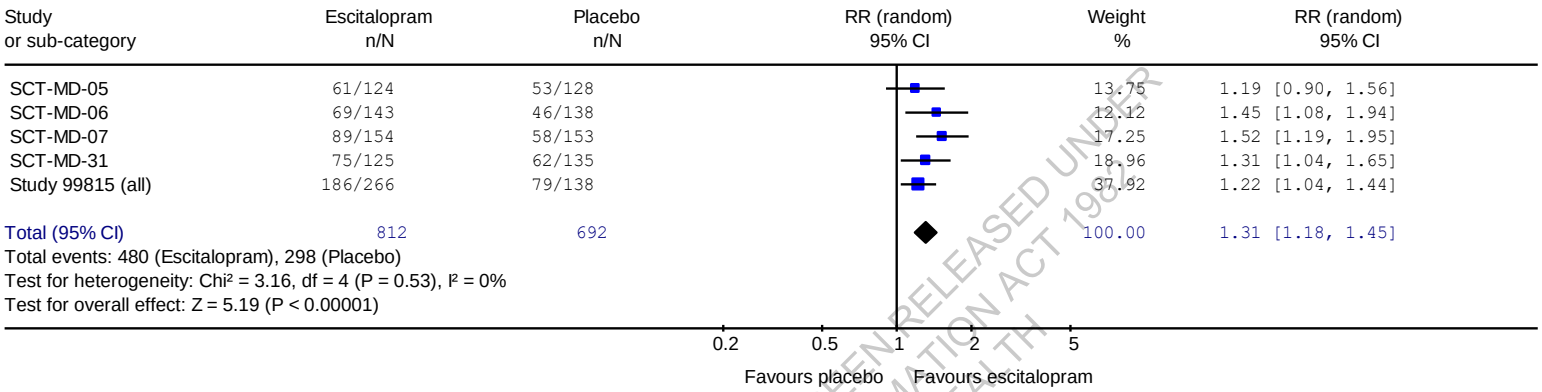


Figure B.6.15: Number and Percentage of Patients with CGI-I ≤2 (ITT LOCF, Study 99815 escitalopram 10 and 20mg arm included)

Review: Escitalopram (Lexapro) - GAD
Comparison: 03 Number of Patients with CGI-I <=2 (ITT LOCF) - secondary endpoint
Outcome: 02 Number of Patients with CGI-I <=2 (ITT LOCF) - final



Clinical Global Impression –Severity (CGI-S)

The meta-analysis results are presented in Figure B.6.16 and Figure B.6.17.

Figure B.6.16: Change in CGI Severity (ITT LOCF, Study 99815 escitalopram 10mg arm included)

Review: Escitalopram (Lexapro) - GAD
Comparison: 04 Change in CGI Severity (ITT LOCF) - secondary endpoint
Outcome: 02 Change in CGI Severity (ITT LOCF) - "Head-to-Head" comparison - final

Study or sub-category	Escitalopram N	Escitalopram Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
SCT-MD-05	124	-1.20(1.12)	128	-0.90(0.91)		21.30	-0.30 [-0.55, -0.05]
SCT-MD-06	143	-1.20(1.15)	138	-0.90(0.95)		22.37	-0.30 [-0.55, -0.05]
SCT-MD-07	154	-1.40(1.13)	153	-0.80(1.01)		23.61	-0.60 [-0.84, -0.36]
SCT-MD-31	125	-1.50(1.21)	135	-1.11(1.18)		16.04	-0.39 [-0.68, -0.10]
Study 99815 (10mg)	134	-1.96(1.20)	138	-1.45(1.20)		16.68	-0.51 [-0.80, -0.22]
Subtotal (95% CI)	680		692			100.00	-0.42 [-0.54, -0.30]
Test for heterogeneity: Chi² = 4 37, df = 4 (P = 0.36), I² = 8.5%							
Test for overall effect: Z = 7.07 (P < 0.00001)							
Total (95% CI)	680		692			100.00	-0.42 [-0.54, -0.30]
Test for heterogeneity: Chi² = 4 37, df = 4 (P = 0.36), I² = 8.5%							
Test for overall effect: Z = 7.07 (P < 0.00001)							

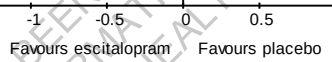
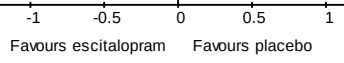


Figure B.6.17: Change in CGI Severity (ITT LOCF, Study 99815 escitalopram 20mg arm included)

Review: Escitalopram (Lexapro) - GAD
Comparison: 04 Change in CGI Severity (ITT LOCF) - secondary endpoint
Outcome: 03 Change in CGI Severity (ITT LOCF) - "Head-to-Head" comparison - final (2)

Study or sub-category	Escitalopram N	Escitalopram Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
SCT-MD-05	124	-1.20(1.12)	128	-0.90(0.91)		21.02	-0.30 [-0.55, -0.05]
SCT-MD-06	143	-1.20(1.15)	138	-0.90(0.95)		22.08	-0.30 [-0.55, -0.05]
SCT-MD-07	154	-1.40(1.13)	153	-0.80(1.01)		23.30	-0.60 [-0.84, -0.36]
SCT-MD-31	125	-1.50(1.21)	135	-1.11(1.18)		15.82	-0.39 [-0.68, -0.10]
Study 99815 (20mg)	132	-1.78(1.10)	138	-1.45(1.20)		17.78	-0.33 [-0.60, -0.06]
Subtotal (95% CI)	678		692			100.00	-0.39 [-0.51, -0.27]
Test for heterogeneity: Chi² = 4.13, df = 4 (P = 0.39), I² = 3.2%							
Test for overall effect: Z = 6.60 (P < 0.00001)							
Total (95% CI)	678		692			100.00	-0.39 [-0.51, -0.27]
Test for heterogeneity: Chi² = 4.13, df = 4 (P = 0.39), I² = 3.2%							
Test for overall effect: Z = 6.60 (P < 0.00001)							



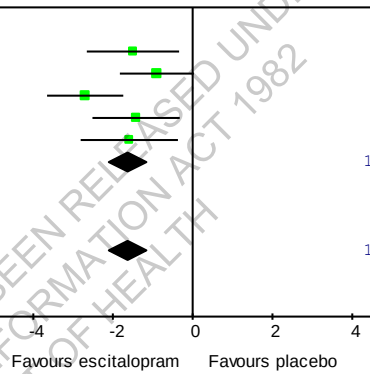
Hospital Anxiety and Depression Scale (HAD) - Anxiety Score

Results from the meta-analysis are presented in Figure B.6.18 and Figure B.6.19.

Figure B.6.18: Change in HAD Anxiety Score (ITT LOCF, Study 99815 escitalopram 10mg arm included*)

Review: Escitalopram (Lexapro) - GAD
Comparison: 09 Change in HAD Anxiety Score (ITT LOCF) - secondary endpoint
Outcome: 02 Change in HAD Anxiety Score (ITT LOCF) - "Head-to-Head" comparison - final

Study or sub-category	Escitalopram N	Escitalopram Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
SCT-MD-05	119	-3.80(4.58)	120	-2.30(4.57)		16.47	-1.50 [-2.66, -0.34]
SCT-MD-06	139	-3.20(3.87)	130	-2.30(3.88)		25.81	-0.90 [-1.83, 0.03]
SCT-MD-07	145	-4.40(4.59)	144	-1.70(3.64)		24.31	-2.70 [-3.65, -1.75]
SCT-MD-31	122	-4.12(4.65)	128	-2.70(4.16)		18.47	-1.42 [-2.52, -0.32]
Study 99815 (10mg)	133	-6.44(5.08)	137	-4.85(5.13)		14.94	-1.59 [-2.81, -0.37]
Subtotal (95% CI)	658		659			100.00	-1.64 [-2.11, -1.16]
Test for heterogeneity: Chi² = 7.40, df = 4 (P = 0.12), I² = 46.0%							
Test for overall effect: Z = 6.81 (P < 0.00001)							
Total (95% CI)	658		659			100.00	-1.64 [-2.11, -1.16]
Test for heterogeneity: Chi² = 7.40, df = 4 (P = 0.12), I² = 46.0%							
Test for overall effect: Z = 6.81 (P < 0.00001)							

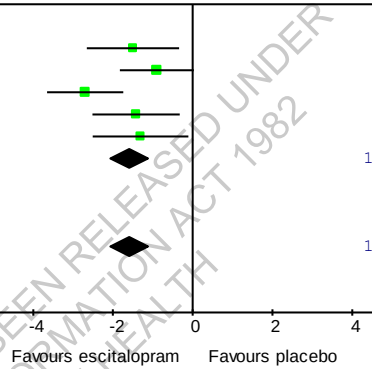


* Study 99815 reported this outcome at Week 12 only, rather than Week 8.

Figure B.6.19: Change in HAD Anxiety Score (ITT LOCF, Study 99815 escitalopram 20mg arm included*)

Review: Escitalopram (Lexapro) - GAD
Comparison: 09 Change in HAD Anxiety Score (ITT LOCF) - secondary endpoint
Outcome: 03 Change in HAD Anxiety Score (ITT LOCF) - "Head-to-Head" comparison - final (2)

Study or sub-category	N	Escitalopram Mean (SD)	N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
SCT-MD-05	119	-3.80(4.58)	120	-2.30(4.57)		16.40	-1.50 [-2.66, -0.34]
SCT-MD-06	139	-3.20(3.87)	130	-2.30(3.88)		25.70	-0.90 [-1.83, 0.03]
SCT-MD-07	145	-4.40(4.59)	144	-1.70(3.64)		24.21	-2.70 [-3.65, -1.75]
SCT-MD-31	122	-4.12(4.65)	128	-2.70(4.16)		18.39	-1.42 [-2.52, -0.32]
Study 99815 (20mg)	132	-6.16(4.92)	137	-4.85(5.13)		15.30	-1.31 [-2.51, -0.11]
Subtotal (95% CI)	657		659			100.00	-1.59 [-2.06, -1.12]
Test for heterogeneity: Chi² = 7.65, df = 4 (P = 0.11), I² = 47.7%							
Test for overall effect: Z = 6.64 (P < 0.00001)							
Total (95% CI)	657		659			100.00	-1.59 [-2.06, -1.12]
Test for heterogeneity: Chi² = 7.65, df = 4 (P = 0.11), I² = 47.7%							
Test for overall effect: Z = 6.64 (P < 0.00001)							



* Study 99815 reported this outcome at Week 12 only, rather than Week 8.

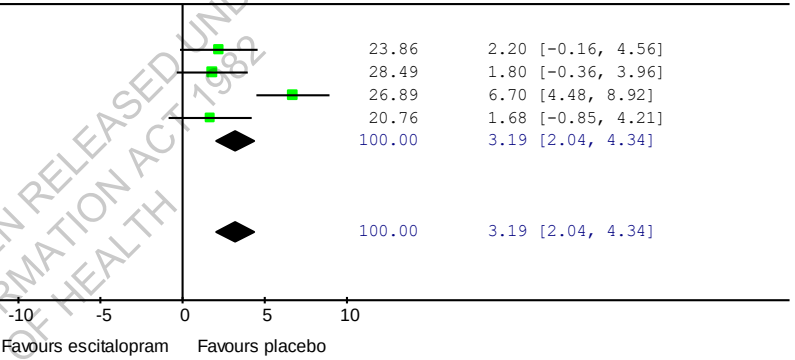
Quality of Life (QOL) Score

Results from the meta-analysis are presented in Figure B.6.20.

Figure B.6.20: Change in Quality of Life (ITT LOCF)

Review: Escitalopram (Lexapro) - GAD
Comparison: 05 Change in Quality of Life (ITT LOCF) - secondary endpoint
Outcome: 01 Change in Quality of Life (ITT LOCF) - "Head-to-Head" comparison - 8 weeks

Study or sub-category	N	Escitalopram Mean (SD)	N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
SCT-MD-05	114	5.40(8.99)	114	3.20(9.18)		23.86	2.20 [-0.16, 4.56]
SCT-MD-06	131	4.80(8.48)	121	3.00(8.96)		28.49	1.80 [-0.36, 3.96]
SCT-MD-07	137	8.40(10.43)	135	1.70(8.14)		26.89	6.70 [4.48, 8.92]
SCT-MD-31	120	6.22(10.39)	128	4.54(9.89)		20.76	1.68 [-0.85, 4.21]
Subtotal (95% CI)	502		498			100.00	3.19 [2.04, 4.34]
Test for heterogeneity: Chi² = 13.23, df = 3 (P = 0 004), I² = 77 3%							
Test for overall effect: Z = 5.42 (P < 0.00001)							
Total (95% CI)	502		498			100.00	3.19 [2.04, 4.34]
Test for heterogeneity: Chi² = 13.23, df = 3 (P = 0 004), I² = 77 3%							
Test for overall effect: Z = 5.42 (P < 0.00001)							



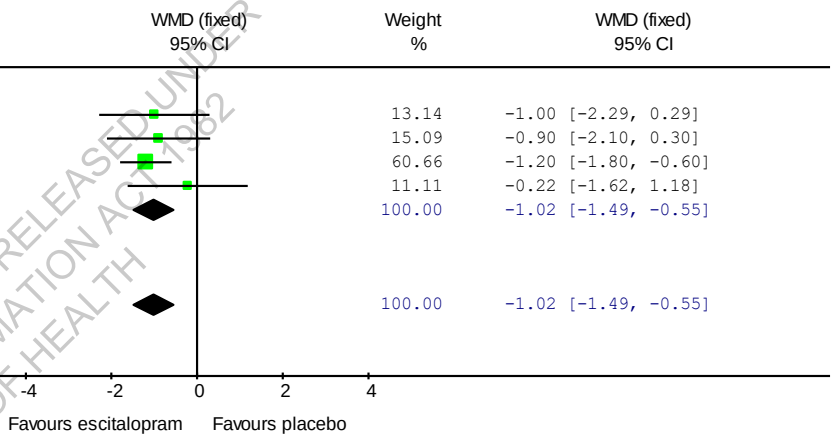
Hamilton Depression Scale (HAMD)

Results from the meta-analysis are presented in Figure B.6.21.

Figure B.6.21: Change in HAMD (ITT LOCF)

Review: Escitalopram (Lexapro) - GAD
Comparison: 06 Change in HAM-D (ITT LOCF) - secondary endpoint
Outcome: 01 Change in HAM-D (ITT LOCF) - "Head-to-Head" comparison - 8 weeks

Study or sub-category	Escitalopram N	Escitalopram Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
SCT-MD-05	116	-2.50(4.65)	115	-1.50(5.32)		13.14	-1.00 [-2.29, 0.29]
SCT-MD-06	132	-3.60(4.84)	122	-2.70(4.93)		15.09	-0.90 [-2.10, 0.30]
SCT-MD-07	140	-1.90(2.38)	137	-0.70(2.70)		60.66	-1.20 [-1.80, -0.60]
SCT-MD-31	118	-2.92(5.59)	124	-2.70(5.53)		11.11	-0.22 [-1.62, 1.18]
Subtotal (95% CI)	506		498			100.00	-1.02 [-1.49, -0.55]
Test for heterogeneity: Chi² = 1.64, df = 3 (P = 0.65), I² = 0%							
Test for overall effect: Z = 4.28 (P < 0 0001)							
Total (95% CI)	506		498			100.00	-1.02 [-1.49, -0.55]
Test for heterogeneity: Chi² = 1.64, df = 3 (P = 0.65), I² = 0%							
Test for overall effect: Z = 4.28 (P < 0 0001)							



B.6.5 Results of key secondary safety outcomes for the individual studies

The key secondary efficacy results for the individual studies are summarised in this section and presented in full Attachment 7.

A summary list of the safety outcomes reported in the escitalopram versus placebo studies is presented in Table B.6.15 below. A summary of these results are presented in Section B.6.5.1 and they are presented in full in Attachment 7.

Table B.6.15: Key secondary safety results for the individual escitalopram vs placebo studies presented in Section B.6.5

Patient-relevant outcome Escitalopram vs placebo	Trial ID					
	SCT-MD-05	SCT-MD-06	SCT-MD-07	SCT-MD-31	99815	99769
Time-point analysed and reported	Week 8	Week 8	Week 8	Week 8	Week 8 & 12	Week 12 & 24
Secondary safety endpoints						
Total study withdrawals	√	√	√	√	√ Week 12	√ at endpoint
Study withdrawals - due to lack of efficacy	√	√	√	√	√ Week 12	√ at endpoint
Study withdrawals – due to AEs	√	√	√	√	√ Week 12	√ at endpoint
Patients with TEAEs	√	√	√	√	√ Week 12	√ at endpoint
TEAEs occurring in ≥5% of patients	√	√	√	√	√ Week 12	√ at endpoint

Key: √ = outcome reported in the Study Report or analysed in the meta-analysis and results presented in Section B.6; NA = not available – not a pre-defined study outcome, therefore data not collected; NR = not reported – data not reported for that outcome ; Changes are all change from baseline; AE = adverse events, CGI-I – Clinical Global Impression Improvement, CGI-S– Clinical Global Impression Severity, HAM-A = Hamilton Anxiety Scale, HAD = Hospital anxiety and depression scale, QOL = Quality of Life Questionnaire Score, TEAE = treatment-emergent adverse events
* Reported as a secondary outcome in this study

The secondary safety outcomes reported in the study comparing placebo with benzodiazepines (Hackett et al.[4]) are summarised in Table B.6.1. The summarised results of these outcomes are presented in Section B.6.5.1 and in full in Attachment 7.

Table B.6.16: Key secondary safety outcomes reported for Hackett et al

Patient-relevant outcome Placebo vs benzodiazepine	Trial ID Hackett et al.
Time-point analysed and reported	Week 8
Secondary safety endpoints	
Total study withdrawals	√
Study withdrawals - due to lack of efficacy	√
Study withdrawals – due to AEs	√

B.6.5.1 Summary of key secondary safety results for the escitalopram versus placebo studies

Study SCT-MD-05, SCT-MD-06, SCT-MD-07 and SCT-MD-31

Patient withdrawals were similar in the escitalopram and placebo groups in all studies, with no significant differences noted. Withdrawals due to lack of efficacy were also similar, with no significant differences noted. Withdrawals due to adverse events were similar also, except for Study SCT-MD-05 where significantly more patients in the escitalopram withdrew due to adverse events (risk difference 0.08, 95% CI 0.02, 0.14). There were no significant differences in the number of treatment-emergent adverse events between the escitalopram and placebo group in any of the studies.

Table B.6.17: Patient withdrawals (total, due to lack of efficacy)

Outcome Timepoint	Trial ID							
	SCT-MD-05		SCT-MD-06		SCT-MD-07		SCT-MD-31	
	Escitalopram	Placebo	Escitalopram	Placebo	Escitalopram	Placebo	Escitalopram	Placebo
n reporting data / N (%)	126 / 128 (98)	128 / 128 (100)	145 / 149 (97)	142 / 145 (98)	158 / 161 (98)	157 / 159 (99)	127 / 131 (97)	136 / 140 (97)
Patient withdrawals:								
Number (%) of patients at:								
Week 8	29 (23.0)	33 (25.8)	27 (18.6)	28 (19.7)	39 (24.7)	34 (21.7)	25 (19.7)	32 (23.5)
Risk difference (95% CI) versus placebo*:								
Week 8	-0.03 (-0.13, 0.08)		-0.01 (-0.10, 0.08)		0.03 (-0.06, 0.12)		-0.04 (-0.14, 0.06)	
Relative risk (95% CI) versus placebo*:								
Week 8	0.89 (0.58, 1.38)		0.94 (0.59, 1.52)		1.14 (0.76, 1.71)		0.84 (0.53, 1.33)	
Patient withdrawals due to lack of efficacy:								
Number (%) of patients at:								
Week 8	2 (1.6)	8 (6.3)	4 (2.8)	0	2 (1.3)	5 (3.2)	3 (2.4)	6 (4.4)
Risk difference (95% CI) versus placebo:								
Week 8	-0.05 (-0.09, 0.00)		0.03 (0.00, 0.06)		-0.02 (-0.05, 0.01)		-0.02 (-0.06, 0.02)	
Relative risk (95% CI) versus placebo:								
Week 8	0.25 (0.06, 1.17)		8.82 (0.48, 162.24)		0.40 (0.08, 2.02)		0.54 (0.14, 2.10)	

Source: Clinical Study Report, Table 1.2 (all studies)
* From Meta-analysis Report

Table B.6.18: Patient withdrawals due to lack of adverse events, Treatment-emergent adverse events occurring in ≥5% of patients

Outcome Timepoint	Trial ID							
	SCT-MD-05		SCT-MD-06		SCT-MD-07		SCT-MD-31	
	Escitalopram	Placebo	Escitalopram	Placebo	Escitalopram	Placebo	Escitalopram	Placebo
n reporting data / N (%)	126 / 128 (98)	128 / 128 (100)	145 / 149 (97)	142 / 145 (98)	158 / 161 (98)	157 / 159 (99)	127 / 131 (97)	136 / 140 (97)
Patient withdrawals due to adverse events:								
Number (%) of patients at:								
Week 8	14 (11.1)	4 (3.1)	8 (5.5)	3 (2.1)	14 (8.9)	8 (5.1)	9 (7.1)	7 (5.1)
Risk difference (95% CI) versus placebo*:								
Week 8	0.08 (0.02, 0.14)		0.03 (-0.01, 0.08)		0.04 (-0.02, 0.09)		0.02 (-0.04, 0.08)	
Relative risk (95% CI) versus placebo*:								
Week 8	3.56 (1.20, 10.51)		2.61 (0.71, 9.65)		1.74 (0.75, 4.03)		1.38 (0.53, 3.59)	
Treatment-emergent adverse events occurring in ≥5% of patients#:								
Number (%) of patients at:								
Week 8	13 (10)	7 (5.5)	10 (6.9)	8 (5.6)	13 (8.2)	6 (3.8)	15 (11.8)	7 (5.1)
Risk difference (95% CI) versus placebo:								
Week 8	0.05 (-0.02, 0.11)		0.01 (-0.04, 0.07)		0.04 (-0.01, 0.10)		0.07 (0.00, 0.13)	
Relative risk (95% CI) versus placebo:								
Week 8	1.89 (0.78, 4.57)		1.22 (0.50, 3.01)		2.15 (0.84, 5.52)		2.29 (0.97, 5.44)	

Source: Clinical Study Report, Table 1.2 (all studies), Table 7.4
* Calculated value, from Meta-analysis Report
# The number of treatment-emergent adverse events is divided by the number of patients to give a % value, however one patient could suffer from multiple TEAEs

Study 99815

The adverse events occurring in Study 99815 are summarised in Table B.6.19 and Table B.6.20. There were no significant differences in patient withdrawals, withdrawals due to lack of efficacy or withdrawals due to adverse events.

Table B.6.19: Patient withdrawals and withdrawals due to lack of efficacy – Study 99815

Outcome Timepoint	Escitalopram 10mg	Escitalopram 20mg	Placebo
n reporting data / N (%)	136 / 136 (100)	133 / 133 (100)	139 / 139 (100)
Patient withdrawals:			
Number (%) of patients at:			
Week 12	18 (13.2)	22 (16.5)	15 (10.8)
Risk difference (95% CI) versus placebo*:			
Week 12	0.02 (-0.05, 0.10)	0.06 (-0.02, 0.14)	
Relative risk (95% CI) versus placebo*:			
Week 12	1.23 (0.64, 2.33)	1.53 (0.83, 2.83)	
Patient withdrawals due to lack of efficacy:			
Number (%) of patients at:			
Week 12	0	2 (1.5)	5 (3.6)
Risk difference (95% CI) versus placebo:			
Week 12	-0.04 (-0.07, 0.00)	-0.02 (-0.06, 0.02)	
Relative risk (95% CI) versus placebo:			
Week 12	0.09 (0.01, 1.66)	0.42 (0.08, 2.12)	

* Calculated value, from Meta-analysis Report

The number of treatment-emergent adverse events is divided by the number of patients to give a % value, however one patient could suffer from multiple TEAEs

Table B.6.20: Patient withdrawals due to adverse events, Treatment-emergent adverse events occurring in ≥5% of patients – Study 99815

Outcome Timepoint	Escitalopram 10mg	Escitalopram 20mg	Placebo
n reporting data / N (%)	136 / 136 (100)	133 / 133 (100)	139 / 139 (100)
Patient withdrawals due to adverse events:			
Number (%) of patients at:			
Week 12	8 (5.9)	14 (10.5)	4 (2.9)
Risk difference (95% CI) versus placebo*:			
Week 12	0.03 (-0.02, 0.08)	0.08 (0.02, 0.14)	
Relative risk (95% CI) versus placebo*:			
Week 12	2.04 (0.63, 6.63)	3.66 (1.24, 10.83)	
Treatment-emergent adverse events occurring in ≥5% of patients#:			
Number (%) of patients at:			
Week 12	11	13	4
Risk difference (95% CI) versus placebo:			
Week 12	0.05 (0.00, 0.11)	0.07 (0.01, 0.13)	
Relative risk (95% CI) versus placebo:			
Week 12	2.81 (0.92, 8.61)	3.40 (1.14, 10.15)	

* Calculated value, from Meta-analysis Report

The number of treatment-emergent adverse events is divided by the number of patients to give a % value, however one patient could suffer from multiple TEAEs

Study 99769

The adverse events occurring in Study 99769 are summarised in Table B.6.21 and Table B.2.1. There were significantly fewer patient withdrawals and withdrawals due to lack of efficacy in the escitalopram group.

Table B.6.21: Patient withdrawals and withdrawals due to lack of efficacy – Study 99769

Outcome Timepoint	Escitalopram	Placebo
n reporting data / N (%)	187 / 187 (100)	188 / 188 (100)
Patient withdrawals:		
Number (%) of patients at:		
Study endpoint	71 (38.0)	136 (72.3)
Risk difference (95% CI) versus placebo*:		
Study endpoint	-34.4% (-43.8% to -24.9%, p<0.001)	
Relative risk (95% CI) versus placebo*:		
Study endpoint	0.52 (0.43 to 0.64, p<0.001)	
Patient withdrawals due to lack of efficacy:		
Number (%) of patients at:		
Study endpoint	40 (21.4)	103 (54.8)
Risk difference (95% CI) versus placebo:		
Study endpoint	-33.4% (-42.6% to -24.2%, p<0.001)	
Relative risk (95% CI) versus placebo:		
Study endpoint	0.39 (0.29 to 0.53, p<0.001)	

* Calculated value, from Meta-analysis Report

The number of treatment-emergent adverse events is divided by the number of patients to give a % value, however one patient could suffer from multiple TEAEs

Table B.6.22: Patient withdrawals due to adverse events, Treatment-emergent adverse events occurring in ≥5% of patients – Study 99769

Outcome Timepoint	Escitalopram	Placebo
n reporting data / N (%)	187 / 187 (100)	188 / 188 (100)
Patient withdrawals due to adverse events:		
Number (%) of patients at:		
Study endpoint	13 (7.0)	16 (8.5)
Risk difference (95% CI) versus placebo*:		
Study endpoint	-1.6% (-7.0% to 3.8%, p=0.572)	
Relative risk (95% CI) versus placebo*:		
Study endpoint	0.82 (0.40 to 1.65, p=0.573)	
Treatment-emergent adverse events occurring in ≥5% of patients#:		
Number (%) of patients at:		
Study endpoint	10 (5.3)	5 (2.7)
Risk difference (95% CI) versus placebo:		
Study endpoint	2.7% (-1.3% to 6.6%, p=0.183)	
Relative risk (95% CI) versus placebo:		
Study endpoint	2.01 (0.70 to 5.77, p=0.194)	

* Calculated value, from Meta-analysis Report

The number of treatment-emergent adverse events is divided by the number of patients to give a % value, however one patient could suffer from multiple TEAEs

Treatment-emergent adverse events

The most commonly occurring treatment-emergent adverse events in each of the studies are detailed in Attachment 7. The most commonly occurring adverse events with escitalopram were headache, nausea, insomnia, somnolence, ejaculation disorder (in males) and fatigue. In the placebo group headache was the most commonly reported adverse events across the studies.

Serious adverse events, including hospitalisations and death

A list of serious adverse events, including hospitalisations and deaths is also provided in Attachment 7.

B.6.5.2 Summary of key secondary safety results for the placebo versus benzodiazepine study (Hackett et al.[4])

Total patient withdrawals and withdrawals due to lack of efficacy and adverse events in the study comparing benzodiazepines and placebo are summarised in Table B.6.23. There were no significant differences between the treatment groups in any of these outcomes.

Table B.6.23: Patient withdrawals, withdrawals due to lack of efficacy and adverse events – Hackett et al.

Outcome Timepoint	Diazepam	Placebo	Source of information (Study Report)
n reporting data / N (%)	89 / NR	97 / NR	
Patient withdrawals:			
Number (%) of patients at:			
Week 8	14 (16)	16 (17)	Table 2, p. 184
Risk difference (95% CI) versus placebo*:			
Week 8	-0.008 (-0.113, 0.098)		
Relative risk (95% CI) versus placebo*:			
Week 8	0.95 (0.49, 1.84)		
Patient withdrawals due to lack of efficacy:			
Number (%) of patients at:			
Week 8	3 (3)	6 (6)	Table 2, p. 184
Risk difference (95% CI) versus placebo:			
Study endpoint	-0.028 (-0.089, 0.033)		
Relative risk (95% CI) versus placebo:			
Week 8	0.55 (0.14, 2.11)		
Patient withdrawals due to adverse events:			
Number (%) of patients at:			
Week 8	2 (2)	4 (4)	Table 2, p. 184
Risk difference (95% CI) versus placebo*:			
Week 8	-0.019 (-0.069, 0.031)		
Relative risk (95% CI) versus placebo*:			
Week 8	0.55 (0.10, 2.90)		

* Calculated value

B.6.6 Results of the meta-analysis of key secondary safety outcomes

Important safety outcomes reported in the meta-analysis included patient withdrawals, withdrawal due to lack of efficacy or adverse events and treatment-emergent adverse events at Study endpoint.

In Study SCT-MD-05, SCT-MD-06, SCT-MD-07 and SCT-MD-31 study endpoint was 8 weeks, while in Study 99815 study endpoint was 12 weeks. The final data was used for all the studies, as Study 99815 did not report safety outcomes at Week 8, (unlike most of the efficacy outcomes that were reported at Week 8 as well as at Week 12).

Due to the differences in study design with Study 99815 (i.e. the fixed escitalopram doses and duration of 12 weeks) the meta-analyses were conducted with and without this study included. No significant differences were seen when the study was or wasn't included, so the meta-analysis results including Study 99815 are presented in this section. The results without Study 99815 are available in the Meta-analysis Report in Attachment 6.

The key safety meta-analysis results are presented Figure B.6.22 to Figure B.6.24. The complete meta-analysis report is provided in Attachment 6.

Summary

Overall the rate of patient withdrawals was the same with escitalopram and placebo (RR 1.01, 95% CI 0.82, 1.24). Patients receiving escitalopram had a higher rate of treatment-emergent adverse events than placebo and more adverse events leading to withdrawal (RR 2.15, 95% CI 1.37, 3.39), as would be expected of an active treatment compared with placebo. However with escitalopram there was a 56% reduction in patients withdrawing from the studies due to lack of efficacy. However this difference was not statistically significant (RR 0.44, 95% CI 0.18, 1.08) due to the increased rate of events leading to withdrawal seen in Study SCT-MD-06 with escitalopram, in contrast to the reduction seen in all the other studies.

Figure B.6.22: Patient withdrawals

Review: Escitalopram (Lexapro) - GAD
Comparison: 11 Safety analyses
Outcome: 02 Patient withdrawals - secondary endpoint - final

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-05	29/126	33/128		22.35	0.89 [0.58, 1.38]
SCT-MD-06	27/145	28/142		18.64	0.94 [0.59, 1.52]
SCT-MD-07	39/158	34/157		25.88	1.14 [0.76, 1.71]
SCT-MD-31	25/127	32/136		19.56	0.84 [0.53, 1.33]
Study 99815 (all)	40/269	15/139		13.57	1.38 [0.79, 2.41]
Total (95% CI)	825	702		100.00	1.01 [0.82, 1.24]

Total events: 160 (Escitalopram), 142 (Placebo)
Test for heterogeneity: Chi² = 2.57, df = 4 (P = 0.63), I² = 0%
Test for overall effect: Z = 0.06 (P = 0.95)

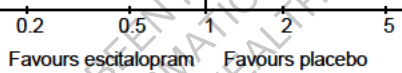


Figure B.6.23: Patients with adverse events leading to withdrawal

Review: Escitalopram (Lexapro) - GAD
Comparison: 11 Safety analyses
Outcome: 04 Patients with adverse events leading to withdrawal - secondary endpoint - final

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
SCT-MD-05	14/126	4/128		17.52	3.56 [1.20, 10.51]
SCT-MD-06	8/145	3/142		12.05	2.61 [0.71, 9.65]
SCT-MD-07	14/158	8/157		29.16	1.74 [0.75, 4.03]
SCT-MD-31	9/127	7/136		22.44	1.38 [0.53, 3.59]
Study 99815 (all)	22/269	4/139		18.83	2.84 [1.00, 8.08]
Total (95% CI)	825	702		100.00	2.15 [1.37, 3.39]

Total events: 67 (Escitalopram), 26 (Placebo)
Test for heterogeneity: Chi² = 2.28, df = 4 (P = 0.68), I² = 0%
Test for overall effect: Z = 3.32 (P = 0.0009)

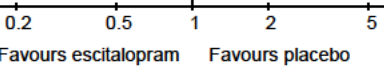
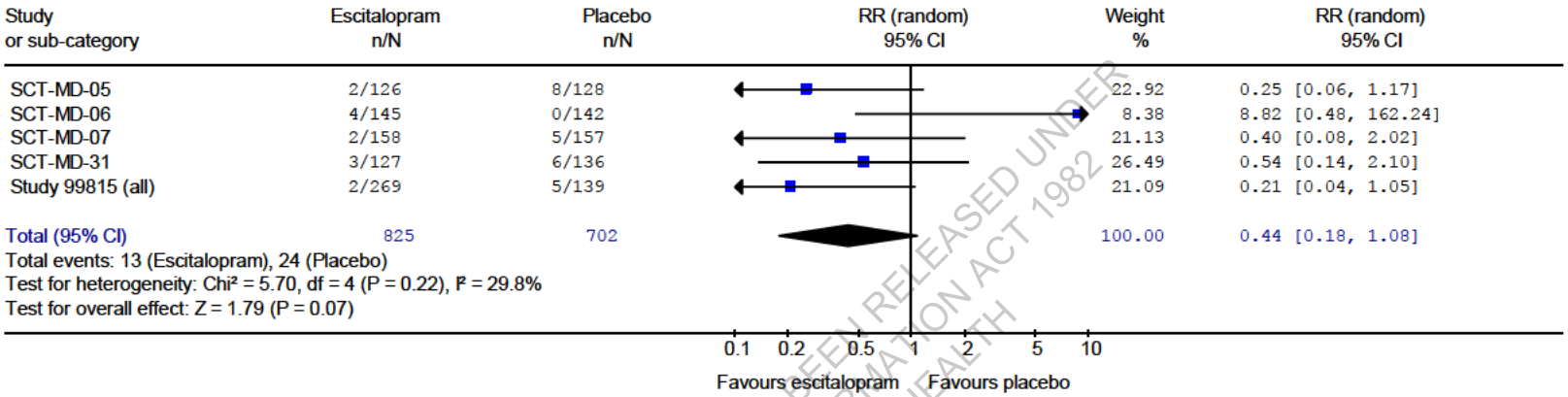


Figure B.6.24: Withdrawals from study due to lack of efficacy

Review: Escitalopram (Lexapro) - GAD
Comparison: 10 Withdrawals from study due to lack of efficacy - secondary endpoint
Outcome: 02 Withdrawals from study due to lack of efficacy - 8 weeks



B.6.7 Results of the supportive study

The results of the supportive, non-randomised, open-label extension study SCT-MD-17 after 24 weeks therapy with open-label escitalopram are presented in Table B.6.24 below. This study included patients who completed Study SCT-MD-05, SCT-MD-06 and SCT-MD-07.

Table B.6.24 : Change from Baseline to Week 24 in efficacy parameters (Mean ± SEM; ITT population, LOCF analysis) for Study SCT-MD-17

Efficacy Parameter*	Escitalopram (n = 521)	
	Baseline	Change at Week 24
HAM-A	13.1 ± 0.3	-3.8 ± 0.3
HAM-A Psychic Anxiety Subscale	7.8 ± 0.2	-2.4 ± 0.2
HAM-A Anxiety Item	1.6 ± 0.04	-0.5 ± 0.1
HAM-A Tension Item	1.6 ± 0.04	-0.5 ± 0.1
CGI-I	2.5 ± 0.1	1.9 ± 0.1
CGI-S	3.0 ± 0.1	-0.8 ± 0.1
HAD Anxiety Subscale	3.8 ± 0.1	-0.9 ± 0.1
QOL	55.9 ± 0.4	3.0 ± 0.4
HAMD	9.0 ± 0.2	-1.8 ± 0.3

CGI–I = Clinical Global Impression – Improvement, CGI–S = Clinical Global Impression – Severity, HAD = Hospital Anxiety and Depression Scale, HAM-A = Hamilton Anxiety Scale, HAMD= Hamilton Depression Scale, QOL = Quality of Life Questionnaire, SEM = standard error of the mean
* Results for additional efficacy parameters (HAD Depression Scale, HAMD Anxiety Subscale, HAM-A Somatic Anxiety Subscale) are not presented in the submission. Results are available in the Study Report Panel 9, p. 30.
Source: Study Report, Panel 9, p. 30.

A sub-set of 259 out of 521 patients in the study completed 36 weeks of escitalopram therapy. These patients received 8 weeks of escitalopram in the randomised phase of the original study (SCT-MD-05, SCT-MD-06 or SCT-MD-07), followed by 24 weeks of open-label escitalopram. The results for these patients are presented in Table B.6.25 below.

Table B.6.25 : Change from Baseline to Week 32 in Efficacy Parameters (Mean ± SEM) – Escitalopram to Escitalopram Population, LOCF analyses

Efficacy Parameter*	Escitalopram (n = 259)
HAM-A	
Baseline (of the lead-in study)	23.0 ± 0.2
Change at Week 8*	-11.0 ± 0.4
Change at Week 32#	-14.0 ± 0.4
HAM-A Psychic Anxiety Subscale	
Baseline (of the lead-in study)	13.4 ± 0.1
Change at Week 8*	-6.4 ± 0.2
Change at Week 32	-8.0 ± 0.3
CGI-I	
Change at Week 8	2.4 ± 0.1
Change at Week 32	1.9 ± 0.1
CGI-S	
Baseline (of the lead-in study)	4.3 ± 0.03
Change at Week 8*	-1.4 ± 0.1
Change at Week 32	-2.0 ± 0.1

CGI–I = Clinical Global Impression – Improvement, CGI–S = Clinical Global Impression – Severity, HAD = Hospital Anxiety and Depression Scale, HAM-A = Hamilton Anxiety Scale, HAMD= Hamilton Depression Scale, QOL = Quality of Life Questionnaire, SEM = standard error of the mean
* End of the lead-in Study
# End of the 24 week open-label extension study
Source: Study Report, Panel 10, p. 31.

Eight weeks treatment with escitalopram (during the double-blind studies) led to substantial improvement in GAD symptomatology. Continuation of treatment for a further 24 weeks led to even further improvement in all efficacy measures. After a total of 32 weeks therapy patients had a mean HAM-A score of 9. This is mean that patients who continued therapy achieve remission from GAD.

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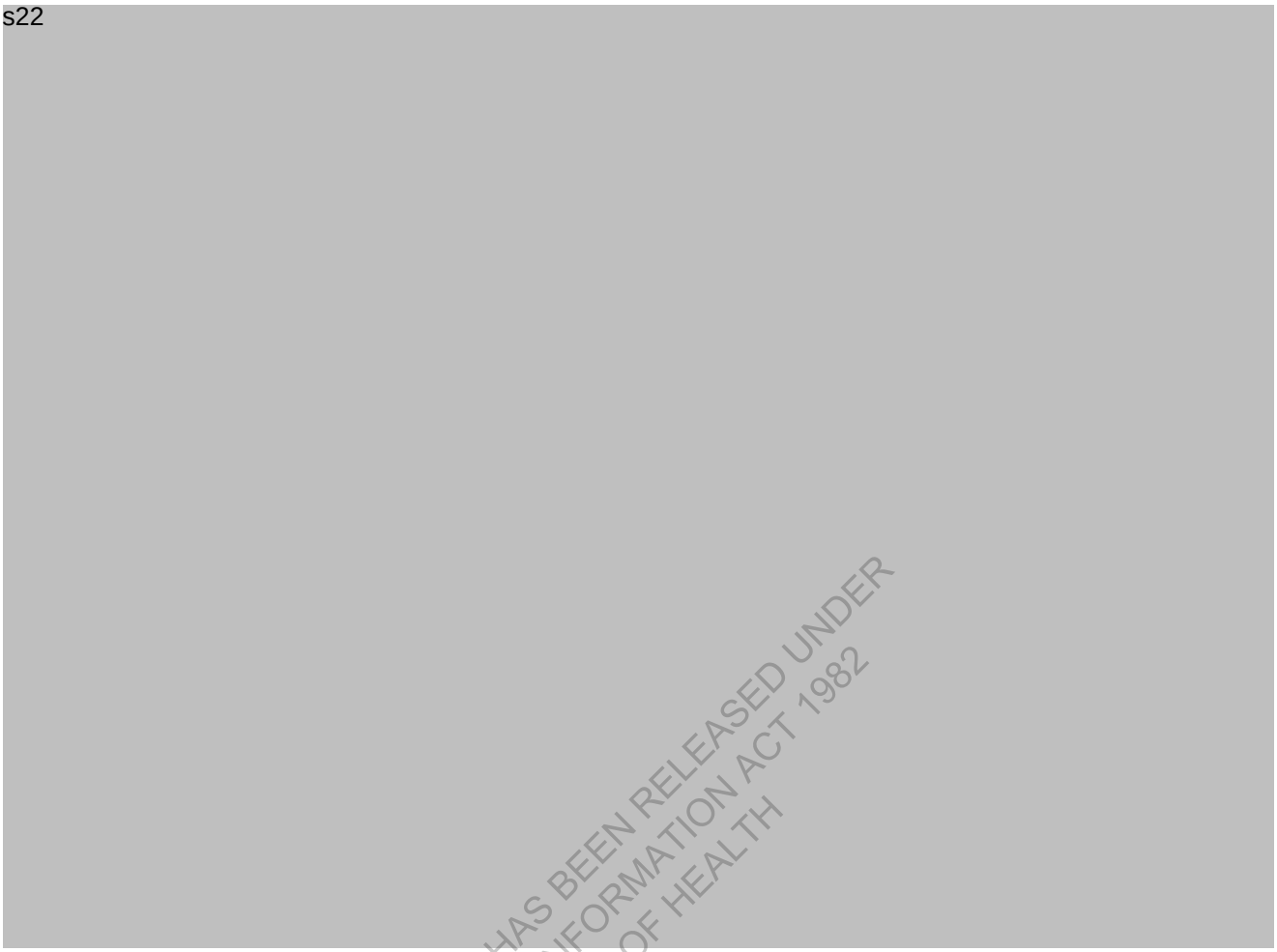

B.6.8 Summary of efficacy and safety data

The results of the randomised, controlled studies and the supportive study all support the efficacy and safety of escitalopram compared with placebo in GAD. All outcomes improved with escitalopram therapy, with many of the improvements being of statistical and clinical significance.

B.6.8.1 Direct comparison of escitalopram versus placebo (comparator 1)

The 6 key randomised, controlled treatment studies all demonstrate the efficacy and safety of escitalopram. The results of the meta-analysis provide an overall view of the efficacy and safety of escitalopram compared with placebo after 8 weeks of therapy. Study 99815 provides information on the efficacy and safety of two different doses of escitalopram (10mg and 20mg daily) for 12 weeks. Safety data for Study 99815 was reported at 12 weeks only. Study 99769 demonstrates the efficacy and safety of a minimum of 24 weeks of escitalopram compared with placebo in preventing relapse, once patients have responded to escitalopram therapy.

Meta-analysis results

The meta-analysis was performed separately using both doses in the fixed dose Study 99815, i.e. 10mg and 20mg with continuous variables. In this section the continuous variable results all refer to the analysis conducted using the 10mg arm, to avoid quoting multiples results for each outcome, while dichotomous outcomes compare both doses.

The primary outcome mean change in the HAM-A total score significantly improved (was reduced) by an additional –2.19 points (-2.93, -1.45). s38 .

The HAM-A Psychic Anxiety sub-scale and Anxiety and Tension Item Scores, as well as the HAD Anxiety Scale are particularly relevant in GAD as they may capture the psychic anxiety aspects of GAD more directly. The results of these three scales were all significantly better with escitalopram (HAM-A Psychic Anxiety Subscale: risk difference –1.70 (95% CI –2.14, -1.26); HAM-A Anxiety Item risk difference –0.34 (95% CI -0.44, -0.24); HAM-A Tension Item risk difference –0.31 (95% CI -0.42, -0.19); HAD Anxiety Score risk difference –1.64 (95% CI –2.11, -1.16).

Analyses of remitters (patients with HAM-A≤7) and responders (patients with HAM-A response ≥50% or CGI≤2) were also reported in some of the studies. There were 44% more HAM-A remitters with escitalopram (RR 1.4, 95% CI 1.10, 1.87). This is an important result, as a HAM-A score ≤7 is an extremely high threshold to achieve, as it effectively represents a patients no longer suffering GAD. There were also significantly more HAM-A responders with escitalopram, with a RR of 1.20 (95% CI 1.03, 1.40). There were 31% more CGI responders with escitalopram (RR 1.31, 95% CI 1.18, 1.45).

All other relevant secondary efficacy endpoints reported (CGI-I score, CGI-S score, QOL score) were also all significantly increased with escitalopram.

There was no significant difference in the number of patient withdrawals (RR 1.01, 95% CI 0.82, 1.24) and withdrawals due to lack of efficacy (RR 0.44, 95% CI 0.18, 1.08). Withdrawals due to adverse events were significantly greater in the escitalopram group (RR 2.15, 95% CI 1.37, 3.39) as were patients with treatment-emergent adverse events (RR 2.00, 95% CI 1.32, 3.02). The treatment-emergent adverse events that occurred were generally mild and previously reported with escitalopram.

Study 99815

The eight week results for Study 99815 were included in the meta-analysis. The 12-week results indicate that the efficacy of escitalopram continued to increase as duration of therapy increased, with greater improvements in the HAM-A Total Score, HAM-A remitters, HAM-A Anxiety and Tension Item, CGI-I score and CGI responders all evident at 12 weeks compared with 8 weeks. The 12 week safety data for this study is included in the meta-analysis.

Study 99769

The primary outcome in Study 99769 was time to relapse. Patients receiving escitalopram for a minimum of 24 weeks double-blind therapy had a significantly lower relapse rate, 19% compared with 56% with placebo, p<0.001; RR 0.39 (95% CI 0.29, 0.53). Time to relapse was significantly greater with escitalopram (Hazard Ratio 4.04, p<0.001). HAM-A total score was also significantly reduced at Week 12 (risk difference –5.96, 95% CI –7.54, -4.38) and reduced further by Week 24 (risk difference –6.61, 95% CI –8.28, -4.94). The results at 24 weeks for all the outcomes were generally greater than at 12 weeks, demonstrating a sustained and continued response to escitalopram.

During the initial 12 weeks of open-label therapy patients either responded well to therapy (reduction in total HAM-A score from 27 to 4 in the escitalopram group and 5 in the placebo group (i.e. the treatment the patients were then randomised to)) or did not respond (change in HAM-A score from 28 to 16 in this patient group). Thus, on average, patients who responded achieved remission from GAD with a HAM-A of <7.

Supportive Study SCT-MD-17

The results of the supportive, non-randomised, open-label extension study demonstrate that patients who received escitalopram in the 8-week treatment studies (SCT-MD-05, SCT-MD-06 and SCT-MD-07) continued to show improved responses after a further 24 weeks of escitalopram therapy. For example, with HAM-A Total Score patients had a mean (± SEM) score of 23.0 ± 0.2 when they were first randomised into the randomised, double-blind 8 week studies. At the end of the 8 weeks of double-blind therapy the mean change in HAM-A scores from baseline were –11.0 ± 0.4. After a further 24 weeks of open-label escitalopram therapy the mean change from baseline was –14.0 ± 0.4. Thus after a total of 32 weeks of escitalopram therapy patients who completed the study had achieved remission from GAD (i.e. a mean HAM-A score of 9)

Further improvements were also noted in HAM-A Psychic Anxiety Scale, CGI-I and CGI-S scores.

B.6.8.2 Indirect comparison of escitalopram versus benzodiazepines (comparator 2)

There are no studies directly comparing escitalopram with benzodiazepines, as benzodiazepines are not longer considered an appropriate treatment for DSM-IV GAD[6]. While escitalopram is indicated for the long-term therapy of GAD, a chronic condition, benzodiazepines are only recommended for the short-term (i.e. less than 6 week) treatment of acute anxiety. The efficacy of escitalopram in GAD increased from 8 to 12 weeks in the treatment clinical trial Study 99815, from 12 to 24 weeks in the relapse prevention Study 99769 and in the open-label extension study from 8 to 24 weeks, demonstrating the appropriateness of escitalopram as a long-term therapy for GAD.

Hackett et al.[4] compared the use of benzodiazepine (diazepam 15mg daily) and placebo. The placebo arm in this study can be used as a common comparator to indirectly compare escitalopram with benzodiazepine.

However the results presented for Hackett et al.[4] in the published paper are limited. The mean change from baseline to Week 8 in HAM-A total score with escitalopram was –14.8 (SD not reported) and –11.7 (SD not reported) with placebo. The difference was reported as not being statistically significantly different. Similarly, there were no significant differences between benzodiazepines and placebo in the results for HAM-A responders (RR 1.24, 95% CI 0.93, 1.65) and CGI-I responders (RR 1.19, 95% CI 0.996, 1.43). In contrast, with escitalopram versus placebo studies the improvement in these outcomes in the meta-analysis were statistically significant different (HAM-A responders RR 1.20, 95% CI 1.03, 1.40; CGI responders RR 1.31, 95% CI 1.18, 1.45).

An indirect statistical comparison was performed using the Z-statistic on the endpoint HAM-A responders (patients with a ≥50% reduction in HAM-A). It was not possible to do a comparison using the primary study endpoint (HAM-A total score) as there were only point estimate results provided in Hackett et al[4]. Full details are provided in the meta-analysis report in Attachment 6. The indirect statistical comparison using placebo as the common comparator showed no statistically significant difference between escitalopram and benzodiazepine at 8 weeks (p=0.8628).

In summary, it is difficult to provide a robust comparison of the efficacy and safety of escitalopram and benzodiazepines due to the lack of direct comparisons and the availability of only one poorly described study comparing benzodiazepine with placebo. The lack of studies of benzodiazepines in DSM-IV GAD is due to the inappropriateness of using benzodiazepines for GAD, other than for the short-term treatment of acute anxiety in GAD. In the one study comparing benzodiazepines and placebo in DSM-IV GAD, there was no significant treatment differences found between the two treatments. In contrast, escitalopram has been shown in a number of well conducted studies to provide a significant improvement in a number of important study outcomes.

B.8 Interpretation of the clinical evidence

Summary

Escitalopram provides superior efficacy and similar safety to the main comparator (placebo). A modelled economic evaluation is presented in Section C. This assessment is based on six well designed and conducted direct comparative randomised, controlled studies. The key study outcome (improvement in the HAM-A Total Score) was significantly improved in the escitalopram treatment groups, compared with placebo in all studies, along with a number of important secondary outcomes. s38

The percentage of patients responding to therapy (based on HAM-A and CGI-I criteria) and achieving remission (based on HAM-A criteria) were also significantly greater with escitalopram, demonstrating the overall superiority of escitalopram therapy across a range of patient-relevant outcomes.

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Escitalopram also provides at least equivalent efficacy to the other comparator (benzodiazepine). This comparison is made via an indirect comparison using placebo as the common comparator. There are no studies comparing the use of escitalopram with benzodiazepines and only one study comparing benzodiazepines with placebo, due to the inappropriateness of benzodiazepine therapy in DSM-IV diagnosed GAD, other than for the treatment of acute anxiety. In the one available

study comparing benzodiazepines with placebo there are no statistically significant differences reported between benzodiazepines and placebo. In contrast, escitalopram is shown to be significantly superior to placebo, across a range of patient-relevant outcomes in a number of well-conducted studies. An indirect statistical comparison between these studies shows no difference.

B.8.1 The level of the evidence

A comprehensive literature review was undertaken, with full details provided in Section B.1 and B.2. Seven studies identified in the literature search and presented in the submission are all double-blind, randomised, controlled, multi-centre, parallel-group **direct** comparisons between escitalopram and placebo (comparator 1). This is generally considered the highest level of clinical evidence available. There are no studies directly comparing escitalopram and benzodiazepines (comparator 2). One double-blind, randomised, controlled, multi-centre, parallel-group study comparing placebo and benzodiazepines in DSM-IV diagnosed GAD was identified to provide an indirect comparison with escitalopram and placebo. In addition, one supportive non-randomised, open-label extension study of escitalopram therapy was identified.

B.8.2 The quality of the evidence

The studies were well designed, conducted and reported, with full details provided in the Clinical Study Reports that have been provided. Full details of the methods of randomisation, and blinding are provided in this submission. Randomisation was by a third party service (the pharmaceutical company). Blinding was maintained throughout the studies, with identical study products provided for each treatment group.

The basis of the analysis was ‘intent to treat’, based on all randomised patients with one valid post-baseline assessment of the primary outcome (a continuous variable). In all cases the results are presented using Last Observation Carried Forward methodology. The flow of participants through each of the studies is clearly identified in Section B.3.

Thus, the level of evidence provided in the submission for the comparison of escitalopram and placebo (comparator 1) is high, with the six studies presented all well conducted, randomised, controlled, double-blind, parallel group studies that provide a direct comparison with the comparator. With comparator 2 (benzodiazepines) an indirect comparison had to be made due to the lack of direct comparative studies. The study comparing placebo with benzodiazepines is also a randomised, controlled trial. However limited results are presented in the published results. Thus, the comparison of escitalopram and benzodiazepines (comparator 2) is made using a much lower level of evidence than the comparison of escitalopram and placebo.

B.8.3 The statistical precision of the evidence and size of effect

Efficacy and safety result data presented in Subsection B.6 for the individual direct randomised trial results and the pooled analyses comparing escitalopram with placebo was able to provide a high level of statistical precision. The primary efficacy results were presented as the difference between escitalopram and placebo in mean change from baseline to study endpoint in HAM-A Total Score (with 95%CI). Secondary efficacy endpoints were presented as difference in mean change from baseline to endpoint with 95% CIs (continuous data), with dichotomous data also being reported as a relative risk (with 95% CI) and NNT (with 95% CI). Safety results were presented with relative risk (with 95%CI) and risk difference (with 95%CI).

The comparison of escitalopram and benzodiazepines (comparator 2) used an indirect comparison and the study comparing benzodiazepines with placebo (the common comparator) provided limited information. While mean change primary efficacy results were provided, no standard deviations or statistical analysis was provided. Thus, the statistical precision of this comparison is much lower.

B.8.4 The size of the effect: Placebo Controlled Trials

The patients in the trials had been sufferers of GAD for 9-13 years and the mean age of onset was 28-30 years. This sample of patients mirrors the epidemiological evidence (see Attachment 2). Patients entering into the trials had a mean HAM-A at baseline between 22.1 to 28.8, thereby, classifying patients as having moderate to severe GAD. At the end of 8 weeks patients on escitalopram achieved a mean HAM-A score ranging from 12.3-13.4 and at 12 weeks 9.45-10.95 (all results were statistically significantly better than placebo). Clinically, this translates into a patient having moderate to severe to moderate GAD and improving to a HAM-A <12 which is considered to be in the "normal" range. This suggests that the results achieved by patients on escitalopram are clinically significant.

Primary Study Outcome – Change in HAM-A Total Score

Table B.8.1 presents a summary of the key outcomes results. s38

In **all** studies, treatment with escitalopram resulted in statistically and clinically significant improvements in HAM-A Total Score, compared with placebo at study endpoint. The mean improvement in the meta-analysis of the treatment studies was –2.19 (95% CI –2.93, -1.45) for escitalopram compared with placebo. The clinical patient relevance of the improvements is discussed in Section B.8.5 below.

Table B.8.1: Summary of Primary and Secondary outcomes

(95% CI)		SCT-MD-05	SCT-MD-06	SCT-MD-07	SCT-MD-31	99815		99769	Hackett
						10mg	20mg	20mg	15mg Diazepam
Difference in mean change HAM-A vs placebo									
	Week 8	-1.6 (-3.2, -0.0)	-1.48 (-2.83, -0.13)	-3.49 (-4 93, -2.04)	-1 52 (-3.28, 0 24)	-2.39 (-4.15,-0.64)	-1.87 (-3.63,-0.12)		
	meta-analysis 8 weeks (10mg from 99815)	-2.19 (-2 93,-1.45)							
	meta-analysis 8 weeks (20mg from 99815)	-2 24 (-2.98, -1.49)							
	Week 12					-2.56 (-4.40,-0.73)	-2.15 (-3.99,-0.31)	-5.96 (-7 54 to -4 38)	
	Week 24							-6.61 (-8 28 to -4 94)	
Patients with CGI≤2:									
	Difference in % of patients with CGI-I<2 vs placebo								
	Week 8	8.0 (-4.0, 20.0)	15.0 (4.0, 26.0)	20.0 (09.0, 31.0)	14.0 (2.0, 26.0)	15.1 (3 9, 26.3)	10.2 (-1 3, 21.7)		12.7 (-0.3, 25.4)
	Week 12					15.3 (4.7, 26.0)	11.2 (0 2, 22 2)		
	Relative Risk vs placebo								
	Week 8	1.19 (0 90, 1 56)	1.45 (1.08, 1.94)	1.52 (1.19, 1.95)	1 31 (1.04, 1.65)	1 26 (1.06, 1 51)	1.18 (0.98, 1.42)		1.19 (0 996, 1.426)
	meta-analysis 8 weeks	**1.31 (1.18, 1.45)**							
	Week 12					1 24 (1.06, 1.45)	1.18 (1.00, 1.39)		
Patients with HAM-A total score ≤7 (HAM-A remitters)									
	Difference in % of patients with HAM-A≤7 vs placebo								
	Week 8				7.0 (-3.0, 18.0)	12.6 (2.0, 23.2)	10.8 (0 3, 21.4)		
	Week 12					18.1 (6.7, 29.4)	13.5 (2.1, 24 9)		
	Relative Risk vs placebo:								
	Week 8				1 32 (0.88, 1 96)	1 58 (1.07, 2 34)	1 50 (1.00, 2.24)		
	meta-analysis 8 weeks					**1.44 (1.10, 1.87)**			
	Week 12					1.61 (1.18, 2 20)	1.45 (1.05, 2.01)		
	NNT with HAM-A≤7 vs placebo								
	Week 8					8 (4,50)	9 (5,333)		
	Week 12					6 (3,15)	7 (4,48)		
Patients with HAM-A total score ≤9 (HAM-A remitters)									
	Difference in % of patients with HAM-A≤7 vs placebo								
	Week 8					16.6 (5.1,28.1)	6.7 (-4.6,18.0)		
	Week 12					12 5 (0.7,24.3)	12.6 (0.7, 24.4)		
	Relative Risk vs placebo:								
	Week 8					1.53 (1.13,2.08)	1.22(0.87,1.69)		
	Week 12					1.29 (1.01,1.64)	1.29 (1.01,1.64)		
	NNT with HAM-A≤9 vs placebo								
	Week 8					6 (4,20)	15 (6,22)		
	Week 12					8 (4,143)	8 (4,99)		
Patients with >50% reduction in HAM-A Total Score (HAM-A responders)									
	Difference in % of patients with ≥50% reduction in HAM-A vs placebo								
	Week 8				11.0 (-2.0, 23.0)	10.5 (-1 3, 22.2)	7.6 (-4.2, 19.5)		11 (-3 5, 25.1)
	Week 12					10.0 (-1.1, 21.2)	8 9 (-2.4, 20.1)		
	Relative Risk vs placebo:								
	Week 8				1 25 (0.97, 1.62)	1 21 (0.98, 1.49)	1.15 (0.92, 1.43)		1.24 (0.93, 1.65)
	meta-analysis 8 weeks					**1.20 (1.03, 1.40)**			
	Week 12					1.16 (0.98, 1 38)	1.14 (0.96, 1.36)		
	NNT								
	Week 8					9 5 (4.5,91)	13 (5.1,24)		
	Week 12					10 (4.7,91)	11 (5,42)		

Secondary Study Outcomes

Table B.8.2 presents a summary of the key secondary outcome results. The results of the key secondary outcomes (proportion of patients with ≥50% improvement in HAM-A (HAM-A responders), proportion of patients with HAM-A≤7 and proportion of patients with HAM-A≤9 (HAM-A remitters), improvement in HAM-A Psychic Anxiety Subscale, HAM-A Anxiety/Tension Item Score, Clinical Global Impression – Improvement and Severity (CGI-I, CGI-S), % patients with CGI-I≤2 (CGI responders), HAD Anxiety scale, QOL score) all improved with escitalopram therapy, with most improvements also being of statistical significance.

More patients receiving escitalopram had treatment-emergent adverse events, with the risk statistically significantly greater in two out of three of the studies. Total patients withdrawals in the two treatment groups were similar, as were withdrawals due to adverse events, with no statistically significant differences between the treatment groups in all studies.

Table B.8.2: Key Secondary Outcome Results

(95% CI)			SCT-MD-05	SCT-MD-06	SCT-MD-07	SCT-MD-31	99815		99769	Hackett
							10mg	20mg	20mg	15mg Diazepam
Relative Risk vs placebo:										
	CGI-I≤2	Week 8	1.19 (0.90, 1.56)	1.45 (1.08, 1.94)	1.52 (1.19, 1.95)	1.31 (1.04, 1.65)	1.26 (1.06, 1.51)	1.18 (0.98, 1.42)		1.19 (0.996, 1.426)
		meta-analysis 8 weeks	1.31 (1.18, 1.45)							
		Week 12					1.24 (1.06, 1.45)	1.18 (1.00, 1.39)		
	HAM-A≤7	Week 8				1.32 (0.88, 1.96)	1.58 (1.07, 2.34)	1.50 (1.00, 2.24)		
		meta-analysis 8 weeks					**1.44 (1.10, 1.87)**			
		Week 12					1.61 (1.18, 2.20)	1.45 (1.05, 2.01)		
	HAM-A≤9	Week 8					1.53 (1.13,2.08)	1.22(0.87,1.69)		
		Week 12					1.29 (1.01,1.64)	1.29 (1.01,1.64)		
	≥50% HAM-A reduction	Week 8				1.25 (0.97, 1.62)	1.21 (0.98, 1.49)	1.15 (0.92, 1.43)		1.24 (0.93, 1.65)
		meta-analysis 8 weeks					**1.20 (1.03, 1.40)**			
		Week 12					1.16 (0.98, 1.38)	1.14 (0.96, 1.36)		
Difference in % of patients with :										
	CGI-I≤2	Week 8	8.0 (-4.0, 20.0)	15.0 (4.0, 26.0)	20.0 (09.0, 31.0)	14.0 (2.0, 26.0)	15.1 (3.9, 26.3)	10.2 (-1.3, 21.7)		12.7 (-0.3, 25.4)
		Week 12					15.3 (4.7, 26.0)	11.2 (0.2, 22.2)		
	HAM-A≤7	Week 8				7.0 (-3.0, 18.0)	12.6 (2.0, 23.2)	10.8 (0.3, 21.4)		
		Week 12					18.1 (6.7, 29.4)	13.5 (2.1, 24.9)		
	HAM-A≤9	Week 8					16.6 (5.1,28.1)	6.7 (-4.6,18.0)		
		Week 12					12.5 (0.7,24.3)	12.6 (0.7, 24.4)		
	≥50% HAM-A reduction	Week 8				11.0 (-2.0, 23.0)	10.5 (-1.3, 22.2)	7.6 (-4.2, 19.5)		11 (-3.5, 25.1)
		Week 12					10.0 (-1.1, 21.2)	8.9 (-2.4, 20.1)		
NNT with :										
	HAM-A≤7	Week 8					8 (4,50)	9 (5,333)		
		Week 12					6 (3,15)	7 (4,48)		
	HAM-A≤9	Week 8					6 (4,20)	15 (6,22)		
		Week 12					8 (4,143)	8 (4,99)		
	≥50% HAM-A reduction	Week 8					9.5 (4.5,91)	13 (5.1,24)		
		Week 12					10 (4.7,91)	11 (5,42)		

B.8.5 The size of the effect: Indirect Trials

As shown in Section B.7 the results presented for Hackett et al.[4] in the published paper are limited. The mean change from baseline to Week 8 in HAM-A total score with escitalopram was –14.8 (SD not reported) and –11.7 (SD not reported) with placebo. The difference was reported as not being statistically significantly different. Similarly, there were no significant differences between benzodiazepines and placebo in the results for HAM-A responders (RR 1.24, 95% CI 0.93, 1.65) and CGI-I responders (RR 1.19, 95% CI 0.996, 1.43). In contrast, with escitalopram versus placebo studies the improvement in these outcomes in the meta-analysis were statistically significant different (HAM-A responders RR 1.20, 95% CI 1.03, 1.40; CGI responders RR 1.31, 95% CI 1.18, 1.45).

An indirect statistical comparison was performed using the Z-statistic on the endpoint HAM-A responders (patients with a ≥50% reduction in HAM-A). It was not possible to do a comparison using the primary study endpoint (HAM-A total score) as there were only point estimate results provided in Hackett et al[4]. Full details are provided in the meta-analysis report in Attachment 6. The indirect statistical comparison using placebo as the common comparator showed no statistically significant difference between escitalopram and benzodiazepine at 8 weeks (p=0.8628).

B.8.6 The clinical importance and patient-relevance of the effectiveness and safety outcomes

HAM-A

The Hamilton Anxiety Scale (HAM-A) (change in the Total Score) is the primary outcome in the treatment studies and a secondary outcome in the relapse prevention trial. According to the ECNP Guidelines[6] it has been used as the gold standard in clinical trials, though it does have shortcomings as it was not developed specifically to measure GAD. The core features of GAD according to DSM-IV are the nervous tension and chronic worrying. These psychic symptoms are captured in part in the HAM-A but the scale has an over-representation of autonomic symptoms. To address this, some studies have concentrated on specific items that contribute to the psychic anxiety factor as being more relevant to DSM-IV GAD. Anxious mood (item 1) and

psychic tension (item 2) are most relevant.[6] The anxiety subscale of the Hospital Anxiety and Depression Scale (HAD) may also capture the psychic anxiety aspects of GAD more directly, though experience with this scale in clinical trials is more limited[6].

s38

GAD responders and remitters

According the ECNP Guidelines[6] 50% reduction in HAM-A Total Score is a widely accepted criteria of response. Remission rate can be a useful measure of efficacy, particularly in long-term treatment studies. Measures of remission based on the HAM-A include a score of less than 10 and less than 8[6, 9] (i.e. percentage of patients with HAM-A ≤9 or ≤7).

Short-term therapy with escitalopram

The HAM-A response rates, based on percentage of patients with a ≥50% reduction, and remission, based on a score of ≤7 are presented in the meta-analysis and for the individual studies in which it was reported. There was a statistically significant 44% increase in HAM-A remitters with escitalopram (RR 1.44, 95% CI 1.10-1.87) in the meta-analysis. It would be fair to also say that given that the sum (total score) indicates the severity of anxiety; and that HAM-A<12 is normal, then patients achieving this can be considered to be remitters. There was also a 20% increase in HAM-A responders with escitalopram compared with placebo, with a RR of 1.20 (95% CI 1.03, 1.40).

Changes in the HAM-A Total Score, psychic anxiety subscale and the individual items relating to anxious mood and psychic tension, as well as the HAD anxiety scale were measured in the studies and are reported in the meta-analysis and the individual study results in Section B.6. Again, there was a clear, significant benefit of escitalopram therapy seen in all the studies and in the meta-analysis. These outcomes capture the core features of GAD, namely nervous tension and chronic worrying which are difficult to control[6].

The meta-analysis provides evidence of the benefits of short-term escitalopram therapy, with significant improvements in all outcomes over 8 weeks of therapy, including in key outcomes including HAM-A total score, HAM-A scales/items relevant to psychic anxiety and HAM-A/CGI-I responders and HAM-A remitters.

The CGI-I (improvement) and CGI-S (severity) have also been used for responder analyses, but the CGI-S is not a sensitive measure and CGI-I score of ≤2 (much or very much improved) is rather insensitive and tends to focus on recent change[6]. Change in percentage of CGI-I responders and CGI-S Score are reported in the meta-analysis and individual study results in Section B.6. The number of CGI-I responders was 31% greater with escitalopram in the meta-analysis (RR 1.31, 95% CI 1.18, 1.45).

Long-term therapy

The benefits of escitalopram therapy are most obvious in the longer-term studies. In the relapse prevention study (99769) patients received an initial 12 weeks of open-label therapy. Many patients achieved a significance response during this time, with mean HAM-A total score reducing from 20 to 5 or 6 in responders. These responder patients were then randomised to receive a further minimum of 24 weeks of therapy. At the end of this additional therapy, patients who continued to receive escitalopram had a mean HAM-A score of 8. A score of 8 indicates remission from GAD, a highly clinically relevant outcome. This was a mean change from baseline of –6.6 greater than with placebo (95% CI –8.2, -4.9). Thus long-term treatment with escitalopram in GAD resulted in the achievement of remission from GAD.

After 36 weeks of treatment with escitalopram in the supportive study SCT-MD-17 patients had a mean HAM-A score of 9. These patients thus also, on average, achieved remission from GAD, an extremely significant outcome further demonstrating the benefits of long-term therapy with escitalopram in GAD.

s22

s22

B.8.7 The consistency of results over the trials presented

The results in the studies presented were generally consistent. All efficacy outcomes improved with escitalopram therapy, with most results achieving statistical significance. This was particularly evident with the primary outcome, difference in mean change in HAM-A Total Score. Results achieved at 12 and 24 weeks were greater than those achieved after 8 weeks of therapy (Study 99815, 99769 and SCT-MD-17). The meta-analysis demonstrated the consistency of results, with a sensitivity analysis being conducted where each study was removed and the impact on the overall results observed. Removing studies resulted in only three small changes of statistical significance, with two of these changes favouring escitalopram (see the Meta-analysis Report in Attachment 6 for full details).

Study 99769 was a relapse prevention study and thus the study design differed from the other two treatment studies. Prior to randomisation into this study, patients had received open-label escitalopram for 12 weeks, with responders then randomised to receive either escitalopram or placebo. Despite this difference in study design, the results occurring in this study were generally consistent with the other studies (in which all patients were randomised to therapy, not specifically responders).

Studies reporting long-term therapy with escitalopram (Study 99769 and SCT-MD-17) showed continued benefit as the duration of therapy increased.

The study comparing benzodiazepines with placebo (Hackett et al.[4]) did not show a significant difference between benzodiazepines and placebo in any of the outcomes reported. The results of this study were thus not consistent with the studies comparing escitalopram and placebo in GAD.

B.8.8 Co-morbidities with GAD – impact on study results

The epidemiology of co-morbidities and GAD is presented in detail in Attachment 2, where an additional literature search was undertaken to identify any relevant papers. As mentioned in the overview of the epidemiology of GAD (Attachment 2), many of the symptoms of GAD overlap with those of depression and other anxiety disorders[17].[18] Major depression frequently co-exists with GAD, presenting clinicians with the diagnostic challenge of distinguishing social withdrawal due to depression from fearful social avoidance. A New Zealand study found that of those followed from 1972 till 2005, where patients with GAD had comorbid depression, 42% of these patients had GAD first.[19] They conclude that this comorbidity seemed to be associated with substantial health burden, as indicated by recurrent course, mental health service use and suicide attempt.

The clinical studies presented in the submission excluded patients with co-morbidities, as recommended in clinical trial guidelines in GAD[6] . The ECNP consensus meeting in March 2000 confirms that where the aim of studies is to establish the efficacy of a medicine in GAD any co-morbidity, especially major depression the commonest comorbidity, should be excluded.[6] Information on the clinical trial evidence regarding escitalopram in treating people with GAD and depression (being the largest comorbidity) is presented in detail in Attachment 10 and summarised below.

No randomised, controlled studies with GAD and depression as a comorbidity were identified in the literature search undertaken specifically looking at comorbidity. The searches identified 21 separate articles. Reasons for exclusions were:

- Not a trial;

- Did not include comorbid population with GAD and MDD (if MDD was an exclusion criterion then the trial was not included), and
- Not an appropriate comparator.

Two relevant, non-randomised studies were identified – Mohamed et al[20] and Olie et al[21] (Table B.8.3 below)

Table B.8.3: Clinical Trial: Anxiety with comorbid depression

	Study Characteristics	Patient Characteristics	Outcomes Measured	Aims of Study
Olie JP et al 2007[21]	Multicentre, open label, non-randomised, prospective, naturalistic setting 12 weeks	Age: 18-82 yrs Females: 64% Dose: 10-20mg MDD: DSM-IV-TR N=790 HAM-A≥20	Primary: MADRS Secondary HAM-A CGI-I CGI-S AEs	To assess any association between changes in the scores of depression rating scales over the study period and the scores of anxiety rating scales at baseline. To evaluate the safety and tolerability of Escitalopram in this patient population. To assess correlations between physician and patient measures of efficacy.
Mohamed S. et al, 2006[20]	Open label, flexible dose, pilot, Psychiatric Service, Veterans Affairs Medical Centre 12 weeks	Age: $\bar{x}$=73yrs Females: 30% Dose: 10-20mg MDD: DSM-IV-TR N=20 HAM-A≥18 MADRS≥22	Primary: MADRS HAM-A Secondary Medical Outcomes SF-36 AEs	To see if escitalopram helps treat elderly patients with comorbidity of major depression and GAD.

The conclusions from these studies were:

- The use of anxiolytics had no impact on the outcome
- Of the 61% of patients experiencing a co-morbidity, results showed that anxiety symptoms as measured with the HAM-A, improved in parallel to the improvement in depressive symptoms, with escitalopram treatment.
- Patients with at least one anxiety disorder had a greater improvement in HAM-A scores than those without comorbid anxiety, but there was no statistically significant difference in the improvement in HAM-A scores as a function of

baseline severity of depression, indicating that comorbid depression did not affect response to treatment of anxiety.

- The remission rate for anxiety symptoms (38.1%) is very close to the 36% reported in a randomized, double-blind clinical trial of escitalopram in patients with pure GAD.[1] Patients with a comorbid anxiety disorder responded well to treatment, particularly those with GAD, SAD, or obsessive–compulsive disorder.
- In a small study in elderly patients with comorbid GAD and MDD Escitalopram was associated with significant improvements in symptoms of anxiety and depression.

B.8.9 Classification of therapeutic relativity

Escitalopram has been demonstrated to be therapeutically superior to the comparator placebo, in Section B.6 and B.8, due to greater comparative effectiveness. The comparative safety is considered similar/non-inferior. While treatment-emergent adverse events are greater with escitalopram than placebo (as would be expected of an active treatment), total patient withdrawals and withdrawals due to adverse events and lack of efficacy are similar in the treatment studies.

It is difficult to compare the efficacy and safety of escitalopram and benzodiazepine (the second comparator). This is due to the inappropriateness of using benzodiazepines for the treatment of a long-term condition such as GAD, other than for the short-term treatment of anxiety. Thus there are no studies directly comparing escitalopram and benzodiazepines, and only one study that can be utilised as an indirect comparator (using placebo as a common comparator).

s22