Pages 1-11 and 23-347 have been redacted in accordance with s22 of the FOI Act

Document 1

Lexapro – Request for ADEC Advice AN: 2004-1296-1

Product: Lexapro (escitalopram as oxalate)
- 5 mg, 10 mg, 15 mg, 20 mg tablets
- oral solution 10 mg/mL (registered following the submission of the application)

Sponsor: Lundbeck Australia P/L

Application: Extension of indication to include - (a) treatment of social anxiety disorder (social phobia); and (b) treatment of generalised anxiety disorder.

Dosage: The proposed dose for both social anxiety disorder and generalised anxiety disorder is 10 mg once daily, increasing to a maximum of 20 mg once daily if clinically indicated. The sponsor proposes long term treatment for both disorders in order to consolidate the response and prevent relapse.

Background

Lexapro (the s-enantiomer of citalopram) is approved for the treatment of major depression. The ADEC has previously considered the drug at its 222nd and 229th meetings. There was initial concern about escitalopram's potential for cardiotoxicity (222nd meeting) arising from the preclinical data. However, these concerns were subsequently addressed by the provision of satisfactory clinical data (229th meeting). The current application seeks to extend the approved indication to include the treatment of social anxiety disorder (SAD) and the treatment of generalised anxiety disorder (GAD). The application includes only clinical data in support of the proposed indications with no new pharmaceutical chemistry/bioavailability or pre-clinical data being provided or required.

The application includes both initial and supplementary clinical data. Supplementary clinical data were submitted to address the clinical evaluator's initial recommendation to reject Lexapro for the treatment of GAD on the basis that the provided data did not include a long-term relapse prevention study for this condition. The supplementary data consisted of such a study. The clinical evaluator subsequently evaluated this study and recommended that Lexapro be approved for both SAD and GAD.

The overseas registration status for both proposed indications at the time of the application is described in the initial clinical evaluation report (p1). However, the overseas registration status of the drug specifically for the treatment of social anxiety disorder and generalized anxiety disorder should be updated in the sponsor's Pre-ADEC Response.

In Australia, the SSRI Aropax (paroxetine) is approved for the treatment of SAD and GAD at a recommended dose of 20 mg/day with the option to increase to 50 mg/day if required. Two other SSRIs (Luvox and Zoloft) are approved for SAD but not GAD, while the SNRI/SSRI (Efexor-XR) is approved for both SAD and GAD.

Efficacy - Social Anxiety Disorder

a. Design

The submission included three pivotal studies provided in support of the application to extend the indication to include the treatment of social anxiety disorder (SAD) [99012, 99270, 99269]. The

studies are well described at pages 2-8 and summarised in Table 1 of the initial clinical evaluation report (CER). **Study 99012** was a short-term, 12-week, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose (escitalopram 10 or 20 mg/day) study, with a 1-week, single-blind, placebo run-in. **Study [99270]** was long-term, 24-week, randomized, double-blind, placebo-controlled, active reference (paroxetine 20 mg/day), fixed-dose escitalopram (5, 10, or 20 mg/day) study, with a 1-week, single-blind, placebo run-in, and a 2-week, single-blind, placebo run-out. **Study [99269]** was a long-term, 24-week, randomized, double-blind, placebo-controlled, fixed-dose (escitalopram 10 or 20 mg/day), relapse-prevention study; preceded by a 12-week, open-label, flexible dose (escitalopram 10 to 20 mg/day) period.

These pivotal studies included patients with a primary diagnosis of SAD according to DSM-IV criteria, with Liebowitz Social Anxiety Scale (LSAS) scores, Clinical Global Impression-Severity (CGI-S) scores, and Sheehan Disability Scale (CDS) scores being used to assess severity inclusion thresholds. The diagnostic inclusion criteria were similar for the three studies but with some minor differences. The criteria are summarized in the initial CER (p2-3). In studies 99012 and 99270 patients were aged between 18 and 65 years while in study 99269 they were aged between 18 and 80 years. Overall, in the double-blind period of these three studies 522 patients were randomized to placebo, 1,187 to escitalopram and 167 to paroxetine.

b. Primary Efficacy Outcomes

In studies 99012 and 99270, the primary efficacy measure was the change from baseline to week 12 in the Liebowitz Social Anxiety Scale (LSAS) total score. In both studies, the primary efficacy analysis was based on comparisons between escitalopram and placebo treated groups using a last-observation carried forward (LOCF) method (see p3, initial CER). The efficacy results are summarized in Table 3 of the initial CER. In **study 99012**, at week 12 the reduction in LSAS total score was statistically significantly greater with escitalopram (10-20 mg/day) than with placebo ($p<0.01$). In **study 99270**, the reduction in LSAS total score was statistically significantly greater at week 12 (from week 2 onwards) for escitalopram 5 mg and 20 mg compared with placebo ($p<0.05$ and $p<0.01$, respectively). However, for escitalopram 10 mg the difference compared with placebo was only seen from week 16 onwards ($p<0.05$). The 10 mg dose did not statistically significantly differ from placebo at the 12 week primary endpoint. The evaluator comments that the lower LSAS baseline scores in the escitalopram 10 mg group compared with the placebo group might have contributed to the failure to show a statistically significant difference between treatments at the 12 week endpoint. In the observed cases analysis, patients treated with escitalopram 20 mg had statistically significantly lower LSAS scores at week 24 than patients treated with paroxetine 20 mg ($p<0.01$).

In **study 99269**, the primary efficacy measure was the time to relapse to SAD in the 24 week double-blind treatment period. Relapse was defined as either an increase in LSAS total score ≥ 10 points relative to the LSAS total score at entry into the double blind period or withdrawal due to lack of efficacy. The statistical analysis was in the population of all randomized patients who took at least one dose of double-blind medicine in the double-blind period. The efficacy results are summarized in Table 3 of the initial CER and show that both time-to-relapse and percentage of patients relapsing statistically significantly favoured escitalopram over placebo. The primary survival analysis of time to relapse also showed a significant advantage for escitalopram compared to placebo ($p \leq 0.001$) (see Attachment 1, "panel 5", of this overview).

c. Secondary Efficacy Outcomes

There were a number of secondary efficacy outcomes and these are described in the initial CER (p3). These outcomes included changes from baseline scores in a number a assessment instruments and responder and remitter analyses. The secondary endpoint, and responder and remitter analyses are summarised in Table 3 of the initial CER. In studies 99012 and 99270, these analyses generally significantly favoured escitalopram over placebo.

d. Pooled Analysis – Studies 99012 & 99720

In a pooled analysis of studies 99012 and 99270 at 12 weeks, escitalopram reduced the LSAS total score to a statistically significant greater extent that placebo (-7.8±1.6 mean±SEM, $p \leq 0.001$). The pooled analysis also included a subgroup analysis which consistently showed statistically significantly lower mean LSAS total scores with escitalopram than with placebo for each of the studied subgroups. The results from the pooled analysis are discussed in the initial CER (p6) and tabulated summaries are provided at "panels" 5 and 10 at Attachment 2.

Efficacy - General Anxiety Disorders

a. Design

Short-Term Studies

The initial submission included **four pivotal short-term studies** in support of the application to extend the indication to include the treatment of generalised anxiety disorder (99815, MD-05, MD-06, MD-07). These studies are well described on pages 9-15 and summarised in Table 1 of the initial CER. **Studies MD-05, MD-06, and MD-07** were all short-term, 8-week, randomised, double-blind, placebo-controlled, flexible escitalopram dose (10-20 mg/day) studies. **Study 99815,** was a short-term, 12-week, randomised, double-blind, fixed-dose study, comparing escitalopram 5 mg, 10 mg, or 20 mg/day with placebo, and using paroxetine 20 mg/day as a reference treatment.

The clinical evaluator states that the studies "used similar" diagnostic inclusion and exclusion criteria. The patient population in the four pivotal, short-term studies included outpatients (18-80 years) with a primary diagnosis of GAD defined by DSM-IV. At study entry, patients were required to have a Hamilton Anxiety Scale (HAMA) total score of ≥ 18 (20 in study 99815), and a score of at ≥ 2 on both tension and anxious mood items of the HMA (which the clinical evaluator considers reflects clinically significant symptomatology). Hamilton Depression Scale (≤ 17) and Montgomery and Asberg Depression Scale (≤ 16) were used to exclude co-morbid major depression. The clinical evaluator describes the inclusion criteria and the use of the rating scales in the initial CER (p9).

Long-Term Studies

The initial submission included one long-term (24-week) study (**MD-20**) designed to compare the efficacy of escitalopram (10-20 mg, flexible dose) to paroxetine (20-50 mg, flexible dose). The study is described on pages 14-15 of the initial CER and summaries in Table 5. The primary efficacy outcome (mean change in HAMA total score from baseline to endpoint at 24 weeks) showed no statistically significant difference between escitalopram and paroxetine. Secondary efficacy endpoints including responder and remitter analyses also showed no statistically

significant difference between treatments. This was a relatively small study involving 121 patients with 60 being randomized to escitalopram and 61 to placebo.

Based on his evaluation of the initial submission the evaluator recommended that the application to register escitalopram be rejected on the basis of inadequate demonstration of long-term efficacy. He commented that "ongoing" **study 99769** could address the issue. The sponsor subsequently submitted this study and it was evaluated as supplementary data by the same evaluator who had reviewed the initial data. Study 99769 was a relapse prevention study in which patients responding to 12-weeks, open-label treatment with escitalopram (10-20 mg) were randomized to 24-76 weeks, double-blind treatment to either escitalopram (20 mg) or placebo followed by a 2-week tapering down period. Patients were aged between 18-65 years with a DSMIV diagnosis of GAD. The GAD had to be of specified severity (total HAMA ≥20 with a score of ≥2 on both tension and anxiety items) with no co-morbid depression (MADRS ≤16). The patient disposition is summarized in Table 1 of the study report (supplementary evaluation).

b. Primary Efficacy Outcomes

Short-Term Studies

The primary efficacy outcome in the four pivotal short-term studies was the change from baseline to endpoint in the HAMA total score, using a LOCF analysis. Comparison between treatment group was by an ANCOVA model, with treatment and study center as factors and the baseline score as a covariate. Efficacy results for **studies MD-05, MD-06, and MD-07,** the three placebo-controlled studies, are summarized in Part B, Table 4. Escitalopram resulted in a statistically significant greater reduction in HAMA total score from baseline than placebo at week 8 in each of the studies. Efficacy results for **study 99815**, the placebo-controlled study with active reference therapy (paroxetine 20 mg/day), are summarized in Part B, Table 5. The results show no statistically significant difference between escitalopram (5, 10, 20 mg) and paroxetine (20 mg), and a statistically significant difference in favour of escitalopram 10 mg, 20 mg compared with placebo. The maximum dose of paroxetine was fixed at 20 mg/day in this study. It is possible that increasing the dose to 50 mg in patients not responding to 20 mg/day might have resulted in better results for paroxetine than were observed.

Long-Term Study

The primary efficacy outcome in long-term **study 99769** was time-to-relapse of GAD defined as either an increase in the HAM total score to ≥ 15 or lack of efficacy judged by the investigator. The Kaplan-Meier plot is provided at Figure 1 of the report on study 99769 (supplementary data). The plot shows that time-to-relapse was statistically significantly longer with escitalopram than with placebo (log-rank p-value < 0.001).

c. Secondary Efficacy Outcomes

Short-Term Studies

There were a number of secondary efficacy outcomes in the four pivotal short-term studies. These are discussed by the clinical evaluator as part of his description of the individual studies. The results for the secondary efficacy outcomes and responder and remitter analyses are summarised for the four pivotal studies in Part B, Tables 4 & 5. The results for the secondary efficacy outcomes support the statistically significant superiority of escitalopram over placebo. In **studies MD-05, MD-06, and MD-07**, four of the total of six responder analyses statistically significantly

favoured escitalopram over placebo while the corresponding number for the remitter analyses were five out of six. In **study 99815**, the results were more patchy with particularly high placebo-response rates being observed for the two responder analyses.

Long-Term Studies

The clinical evaluator describes the results from a number of other efficacy outcomes in addition to the primary efficacy outcome. It is assumed that these additional outcomes are secondary outcomes. The proportion of patients who relapsed was significantly higher with placebo (56%) than with escitalopram (19%), and patients receiving placebo had a four-fold greater risk of relapse than patients receiving escitalopram.

d. Pooled Analysis – Short-Term Studies (MD-05, MD-06, MD-07)

On page 13 of the initial CER, the evaluator describes the efficacy results from a pooled analysis of the three, 8-week, placebo-controlled studies in the ITT, LOCF patients. In this study, the least square mean HAMA total score at endpoint was 15.2 for placebo (n=419) and 13.0 for escitalopram (n=421); treatment difference mean±SEM = -2.3, $p \leq 0.001$. The majority of the secondary endpoint analyses also showed statistically significant better results for escitalopram compared with placebo. The pooled subgroup analyses also showed that escitalopram produced statistically significantly better results than placebo for each of the analyses. The results from the pooled analysis are summarized at Attachment 3, "Panel 23" (efficacy results) and "Panel 24" (efficacy results in subgroups).

Safety – Social Anxiety Disorder & General Anxiety Disorder

The clinical evaluator has provided a summary of the adverse drug reactions (ADRs) reported in the SAD and GAD short-term studies. The majority of the reported ADRs occurred statistically significantly more frequently with escitalopram than with placebo. The most commonly occurring ADRs associated with escitalopram were nausea, insomnia, fatigue, somnolence, diarrhoea, increased sweating, dizziness, and ejaculation disorder.

The clinical evaluator has also reviewed the specific safety data from each of the submitted studies. In study 99720 (SAD), there were two cases of attempted suicide in patients taking escitalopram and one completed suicide in a patient taking placebo. In MID-17 (GAD), there was one completed suicide and one attempted suicide in patients taking escitalopram. In the SAD studies, the clinical evaluator comments that significant withdrawal symptoms were noted following abrupt discontinuation of escitalopram at both 12 and 24 weeks.

The clinical evaluator comments that the adverse event profile in the SAD studies "was consistent with previously published data for clinical trials in Major Depression". He also comments that the "frequency and profile of adverse evens [relapse prevention study in GAD] was similar to that of previous trials in this indication and in Social Anxiety Disorder".

The clinical evaluator has also reviewed the safety data from the long-term studies. In study 99769, he comments that the frequency and profile of adverse events was similar to those of the other clinical trials (short-term) for GAD and also for SAD.

Issues

a. Social Anxiety Disorder – Efficacy

The short-term (12-week) efficacy of escitalopram at the proposed doses for the treatment of SAD has been satisfactorily established in two, placebo-controlled pivotal studies (99012, 99270). **In study 99012**, escitalopram (n=177) at a dose of 10-20 mg/day lowered the total LSAS score at 12 weeks (primary efficacy measure) to a statistically greater extent than placebo (n=176). The secondary efficacy measures and responder analysis (but not the remitter analysis) in study 99012 supported the positive primary efficacy findings. **In study 99720**, escitalopram at doses of 5 mg/day (n=166) and 20 mg/day (n=163), but not 10 mg/day (n=164), lowered the total LSAS score as 12 weeks (primary efficacy measure) to a statistically significant greater extent than placebo (n=165). Most of the secondary efficacy outcome, responder and remitter analyses at 12 weeks for the three doses of escitalopram statistically significantly favoured escitalopram at doses of 5 mg, 10 mg, and 20 mg daily over placebo. Furthermore, in study 99270 the 24 week outcome data for LSAS and other outcome measures statistically significantly favoured the three doses of escitalopram over placebo. In addition, in study 99270 escitalopram 20 mg (n=163) reduced the LSAS total score at week 24 to a statistically significantly greater extent than paroxetine 20 mg (n=167) in the observed cases analysis.

The long term (24-week) efficacy of escitalopram 10-20 mg daily has been satisfactorily demonstrated in one relapse prevention study (**study 99269**). In this study, escitalopram (n=190) at both 10 and 20 mg/day statistically significantly delayed the onset of relapse compared to placebo (n=181) over 24-weeks in patients who had previously responded to 12 weeks of escitalopram. The study suggests that efficacy can be maintained by escitalopram 10-20 mg/day for 6-9 months in responders.

The responder data from the two short-term pivotal studies suggests that the number needed to treat (NNT) with escitalopram before response can be expected is 5-10 patients (absolute responder differences being of the order of 10-20%). Overall remitter data suggests that the NNT with escitalopram before remission can be expected is about 5 patients (absolute differences being variable among pair-wise comparisons but generally of the order of about 20%). The relapse date in the long term studies shows that the absolute difference in the relapse rate between escitalopram and placebo was 28% over the 24 week double-blind period. These figures suggest that the NNT to prevent a relapse occurring in the 6 months following an acute response to treatment is of the order of 3 to 4 patients.

In the Pre-ADEC Response the sponsor is requested to provide tabulated summaries of the 12-week primary efficacy variables (mean difference in LSAS total score between escitalopram and placebo **with 95% confidence intervals**) in the LOCF population for studies 99012 and 99270. In addition, tabulated summaries should also be provided for the mean difference in LSAS total score **with 95% confidence intervals** at week 24 for pair-wise comparisons of escitalopram (all three doses) versus placebo, paroxetine 20 mg versus placebo, and escitalopram 20 mg versus paroxetine 20 mg in the LOCF population. The sponsor is also requested to indicate how many patients older than 65 years with SAD were treated with escitalopram.

b. General Anxiety Disorder – Efficacy

The short-term (8-week) efficacy of escitalopram at the proposed doses for the treatment of GAD has been satisfactorily demonstrated in three pivotal, placebo-controlled studies (MD-05, MD-06, MD-07). In each of these three studies, escitalopram (10-20 mg/day) lowered the HAMA total

score from baseline to endpoint (the primary efficacy endpoint) to a statistically significantly greater extent than placebo. The secondary efficacy outcomes and responder and remitter analyses supported the statistically significant superiority of escitalopram (10-20 mg) over placebo. These three studies included 840 patients of whom 421 received escitalopram (10-20 mg) and 419 placebo.

The short-term (12-week) study (99815) comparing escitalopram (5 mg, 10 mg, 20 mg) with placebo and paroxetine (20 mg) satisfactorily established the statistically significant superiority of escitalopram (10 mg & 20 mg) over placebo on the primary efficacy endpoint of reduction in HAMA total score from baseline to endpoint. Overall, the positive results for the primary efficacy outcomes for escitalopram 10 mg and 20 mg were supported by the results for the secondary efficacy outcomes and responder and remitter analyses. Furthermore, the primary efficacy analysis statistically significantly favoured escitalopram 10 mg over paroxetine 20 mg. The comparisons between escitalopram 5 mg & 10 mg and paroxetine 20 mg for all efficacy endpoints were not statistically significant. The study included 674 patients of whom 134 were randomised to escitalopram 5 mg, 134 to 10 mg escitalopram, 132 to 20 mg escitalopram, 136 to paroxetine 20 mg and 138 to placebo.

The long-term (12-week open label, followed by 24-76 weeks relapse prevention study (**study 99769**) satisfactorily established that the time-to-relapse in patients treated with escitalopram (n=187 randomised, n=116 completed) was statistically significantly longer than patients treated with placebo (n=188 randomised, n=52 completed). The number of patients withdrawing from the study because of loss of efficacy was three-fold higher with placebo (n=96) than with escitalopram (n=32).

The responder data (≥ 50% decrease in HAMA) from the three pivotal short-term studies suggests that the NNT with escitalopram before a response can be expected is about 5 patients (the absolute difference in the responder rate varies among the three studies but averages about 18%). The relapse data in the long-term studies suggest that the NTT to prevent a relapse over 24-76 weeks is about 3 patients (absolute difference between escitalopram and placebo is 37%). Examining the data in this way suggests that escitalopram is more efficacious in both the short and long term for the treatment of GAD than for the treatment of SAD.

In the Pre-ADEC Response, the sponsor is requested to provide a tabulated summary of the mean difference in the mean change in HAMA total score at endpoint between escitalopram and placebo **with 95% confidence intervals** in the LOCF population for studies MD-05, MD-06, and MD-07. In addition, a similar tabulated summary of this efficacy outcome should also be provided for pair-wise comparisons of escitalopram (all three doses) versus placebo, paroxetine 20 mg versus placebo, and escitalopram 20 mg versus paroxetine 20 mg in the LOCF population for study 99815. The sponsor is also requested to indicate how many patients older than 65 years with GAD were treated with escitalopram.

c. Safety – Social Anxiety Disorder & Generalised Anxiety Disorder

The safety profile of escitalopram for the treatment of SAD and GAD appears similar to, and consistence with, the known profile of the drug for the treatment of MDD. No new safety concerns appear to have arisen. However, in the Pre-ADEC response the sponsor should specifically comment on the incidence of the AEs of suicidality (suicidal thinking and/or suicidal behaviour), completed suicides, disturbed thinking, and aggression in both escitalopram and placebo in the SAD and GAD data set. In addition, the sponsor should also comment on cardio-vascular AEs reported in the short-term and long-term SAD and GAD data sets. This comment

should include escitalopram versus placebo comparisons on the incidence of myocardial infarction, cardiac angina, cardiac arrhythmias (including QTc prolongation and Torsades de Pointe), hypertension, cerebrovascular haemorrhage, cerebrovascular infarction, and cerebrovascular transient ischaemic attacks.

d. Product Information

The clinical evaluator has made a number of suggestions relating to the PI (initial clinical evaluation report, page 19). Some of these suggestions will now need to take into account the long-term relapse prevention study provided as supplementary data. The clinical trials section should include a description of the long-term relapse prevention study in GAD. The evaluator has made specific recommendations relating to the wording of withdrawal symptoms found under the "Precautions" and the "Dosage and Administration" sections of the PI, and these should be implemented. In its Pre-ADEC response, the sponsor should expressly state if it proposes to include any adverse reactions in the PI from the SAD/GAD data set. and, if so, these should be clearly identified in the response. The PI provided with the Pre-ADEC response should be the currently approved PI and all proposed additions should be clearly indicated by underlining and all proposed deletions by strike-through.

Proposed Action

I proposed to approve LEXAPRO (escitalopram) for the treatment of Social Anxiety Disorder (Social Phobia), and for the treatment of Generalised Anxiety Disorder.

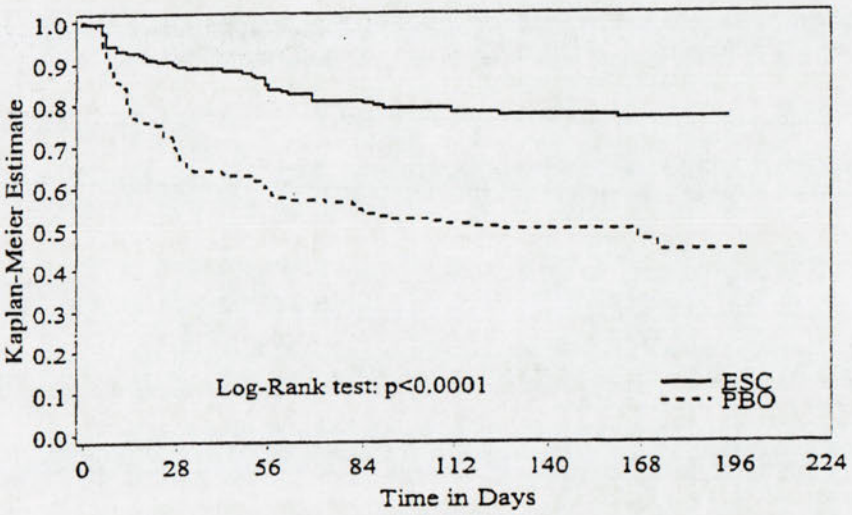
The ADEC's advice is requested on my proposed actions.

s22 [redacted]

Delegate of the Secretary
14 June 2005

Attachment 1

Panel 5 Analysis of Time to Relapse (ITT) - Double-blind Period - Study 99269



Attachment 2

Panel 9: SAD[a] Pooled Analysis - Efficacy Results (ITT, LOCF, Week 12)

Efficacy Parameter[b]	PBO (n=341)	ESC (n=670)	Treatment Difference ESC *versus* PBO (mean ± SEM)
Primary endpoint:			
LSAS total score	66.4	58.6	-7.8 ± 1.6***
Secondary endpoints:			
LSAS fear/anxiety subscale score	35.5	31.1	-4.3 ± 0.8***
LSAS avoidance subscale score	31.1	27.5	-3.6 ± 0.9***
SDS work score	4.9	4.0	-0.9 ± 0.2***
SDS social life score	4.7	4.0	-0.7 ± 0.2***
SDS family life score	2.9	2.5	-0.4 ±0.1**
CGI-S score	3.7	3.3	-0.4 ± 0.1***
CGI-I score	2.8	2.4	-0.3 ± 0.1***

Statistically significantly different from placebo: ** p≤0.01; *** p≤0.001
a 12-week data from studies 99012 and 99270.
b Least Squares Mean at Week 12.

Panel 10: SAD[a] Pooled Analysis – Efficacy Results in Subgroups – LSAS Total Score (ITT, LOCF, Week 12)

Subgroup (n ESC; n PBO)	PBO[b] (n=341)	ESC[b] (n=670)	Group Difference Change Score ESC *versus* PBO (mean ± SEM)
Severity of SAD at baseline			
Severe SAD (LSAS≥95) (n=289; n=167)	79.7	70.3	-9.4 ± 2.7***
Less severe SAD (LSAS<95) (n=381; n=174)	57.4	49.9	-7.5 ± 2.2***
Age[c]			
Age≥55 years (n=42; n=23)	70.7	58.7	-12.0 ± 7.9
Age<55 years (n=628; n=318)	66.1	58.6	-7.5 ± 1.7***
Sex			
Women (n=342; n=166)	67.4	57.6	-9.8 ± 2.5***
Men (n=328; n=175)	65.4	58.8	-6.6 ± 2.4**
Duration of SAD			
Duration of SAD≥18 years (n=369; n=179)	67.2	59.7	-7.5 ± 2.5**
Duration of SAD<18 years (n=301; n=162)	65.3	55.9	-9.4 ± 2.4***
Comorbidity with depression			
Comorbidity (MADRS>12) (n=81; n=59)	79.7	66.2	-13.5 ± 4.1**
No comorbidity (MADR≤12) (n=589; n=282)	64.4	57.7	-6.7 ± 1.8***

Statistically significantly different from placebo: ** p≤0.01; *** p≤0.001
a 12-week data from studies 99012 and 99270.
b Least Squares Mean at Week 12.
c 55 years of age was chosen as the cut-off since there were too few patients ≥ 60 years.

Attachment 3

Panel 23: GAD Pooled Analysis [a] – Efficacy Results (ITT, LOCF, Week 8)

Efficacy Parameter [b]	PBO (n=419)	ESC (n=421)	Treatment Difference ESC vs PBO (mean±SEM)
Primary endpoint:			
HAMA total score	15.2	13.0	-2.3 ± 0.4***
Secondary endpoints:			
HAMA psychic anxiety subscale score	9.4	7.6	-1.8 ± 0.3***
CGI-S score	3.4	3.0	-0.4 ± 0.1 ***
CGI-I score	2.8	2.5	-0.3 ± 0.1***
HAMA item I (anxious mood)	1.9	1.6	-0.4 ± 0.1 ***
HAMA item 2 (tension)	1.9	1.6	-0.3 ± 0.1***
HAMA somatic anxiety	5.8	5.3	-0.5 ± 0.2*
HAMD anxiety [c]	4.3	3.5	-0.8 ± 0.1***
HAD anxiety subscale score	10.7	9.0	-1.7 ± 0.3***
Covi total score [c]	5.1	4.2	-0.9 ± 0.1 ***
QoL total score c	54.0	57.7	3.8 ± 0.6***

Statistically significantly different from placebo: * p≤0.05; *** p≤0.001
a Studies MD-05, MD-06, MD-07
b Least Squared Mean at Week 8
c Observed Cases

Panel 24: GAD Pooled Analysis [a] – Efficacy Results in Subgroups – HAMA Total Score (ITT, LOCF, Week 8)

Efficacy Parameter [b]	PBO (n=419)	ESC (n=421)	Treatment Difference ESC vs PBO (mean±SEM)
Severity of GAD at baseline			
HAMA<22 (less severe GAD) (n=177; n=190)	13.0	9.7	-3.3 ± 0.6***
HAMA≥22 (severe GAD) (n=244; n=229)	16.8	14.8	-2.0 ± 0.6**
Age			
Age≥60 years (n=29; n=28)	16.4	12.4	-4.0 ± 1.8*
Age<60 years (n=392; n=391)	15.1	13.0	-2.1 ± 0.4***
Sex			
Women (n=242; n=230)	15.8	13.0	-2.9 ± 0.6***
Men (n=179; n=189)	14.7	13.1	-1.7 ± 0.7*
Duration of GAD			
≥6 years (n=208; n=208)	15.0	12.8	-2.3 ± 0.6***
<6 years (n=213; n=211)	16.0	13.4	-2.6 ± 0.7***
Comorbidity with depression			
Comorbidity (HAMD>12) (n=222; n=222)	16.3	14.4	-2.0 ± 0.6**
No comorbidity (HAMD≤12) (n=199; n=197)	14.3	11.3	-3.0 ± 0.6***

Statistically significantly different from placebo: * p≤0.05; p≤0.01; *** p≤0.001
a Studies MD-05, MD-06, MD-07
b Least Squared Mean at Week 8