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ORIGINAL RESEARCH

Long-term administration of escitalopram in patients with social anxiety disorder in Japan

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Purpose: To investigate the safety, tolerability, and effectiveness of escitalopram in patients with social anxiety disorder in Japan.

Methods: A 52-week, open-label study was conducted in Japanese patients with social anxiety disorder with a total score ≥60 on the Liebowitz Social Anxiety Scale – Japanese Version (LSAS-J) and ≥4 on the Clinical Global Impression – Severity Scale. Escitalopram 10 mg/day was administered for the first week and could be increased to 20 mg/day.

Results: The study included 158 patients: 81.0% (128/158) completed 52 weeks of escitalopram treatment, 68.4% (108/158) increased their dose to 20 mg/day, and 56.3% (89/158) remained on 20 mg/day. Adverse drug reactions were reported by 57.6% (91/158) of patients. The most common (incidence ≥10%) were somnolence and nausea. The incidence of adverse drug reactions was similar in extensive and poor metabolizers of cytochrome P450 2C19. No adverse drug reactions increased in incidence by >5% after week 12. The incidence of serious adverse events was 1.3% (2/158). No deaths occurred. The LSAS-J total scores improved until week 52. The LSAS-J response rate (≥30% improvement in LSAS-J) was 69.0%, the Clinical Global Impression – Improvement Scale response rate (≤2) was 73.0%, and the LSAS-J remission rate (≤30) was 27.0%.

Conclusion: In this first 52-week clinical study of social anxiety disorder, escitalopram 10–20 mg/day was safe, well tolerated, and effective in Japanese patients.

Keywords: escitalopram, Japanese, long-term study, social anxiety disorder, selective serotonin reuptake inhibitors

Introduction

Social anxiety disorder (SAD) is a psychiatric disorder characterized by considerable fear of social situations or activities, in which the patient could become the focus of attention of others, and by avoiding of anxiety-provoking situations.[1] SAD is generally considered a chronic disorder.[2] Because patients with SAD tend to become socially isolated through continued avoidance of social situations, SAD affects their educational, professional, and economic status[3] resulting in considerable loss not only to the patients themselves and their families, but also to society overall. Additionally, anxiety disorders, including SAD, are risk factors for suicidal ideation and suicide attempts and these risks are increased further by concurrent mood or anxiety disorders.[4]

In Japan, *taijin-kyofu* (TK) is a syndrome similar to SAD characterized by interpersonal sensitivity and fear and avoidance of interpersonal situations. The *Diagnostic and Statistical Manual of Mental Disorders-5* emphasized in the "Culture-Related Diagnostic Issues" section on SAD that "The syndrome of *taijin kyofusho* (eg, in Japan and Korea) is often characterized by social-evaluative concerns, fulfilling the criteria for social anxiety disorder."[1] TK has two subtypes – the "sensitive"

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and the "convinced" (c-TK; also called the "offensive" subtype).[5] The common characteristics of c-TK are: 1) patients firmly believe that they have serious shortcomings, such as unpleasant body odor, inadequate eye expression, perceived physical defects, or stiff facial expression; 2) patients intuit from the behavior and actions of others that these shortcomings exist; and 3) patients perceive that these defects make others feel unpleasant and therefore must be corrected or removed by all means.[6]

Treatments for SAD include pharmacotherapy and psychotherapy, which may be used alone or in combination.[7] Selective serotonin reuptake inhibitors or serotonin/noradrenaline reuptake inhibitors are considered the first-line pharmacotherapy, and their efficacy has been demonstrated in double-blind studies.[7–12] A long-term perspective is needed when treating SAD, and if a drug recommended by the treatment guidelines and/or treatment algorithms proves effective, treatment should be continued for 12 months in patients responsive to treatment.[8,9,11]

Escitalopram (ESC) is metabolized primarily by cytochrome P450 (CYP) 2C19, and patients are classified by CYP2C19 polymorphisms into either extensive metabolizers (EMs) or poor metabolizers (PMs). The proportion of PMs varies with ethnicity, being 2%–5% in Caucasians, but 15%–23% in Asians, including Japanese.[13] In a clinical pharmacokinetic study conducted in Japan, the $AUC_{0-\infty}$ of ESC in plasma in CYP2C19 EM subjects was about twice that in PM subjects.[14]

In this study, ESC was administered to patients with SAD in Japan for 52 weeks using flexible doses of 10–20 mg/day to investigate the safety and efficacy of long-term use of ESC, focusing on stratified analysis by CYP2C19 genotype.

Methods

Study design

This multicenter, open-label, flexible-dose, long-term study was conducted in 50 centers in Japan from December 2012 to October 2014. All centers obtained approval from their respective institutional review boards before initiating study treatment. This study complied with the Declaration of Helsinki and the Japanese Ministerial Ordinance on Good Clinical Practice for Drugs. Investigators obtained written informed consent from all patients who participated in this study. Patients' anonymity was preserved.

Study patients

Patients with SAD as their primary diagnosis according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition – Text Revision[15] were eligible for this study. Patients were diagnosed using the Mini-International Neuropsychiatric Interview Japanese version 5.0.0.[16] Eligible patients of either sex were aged ≥18 and ≤64 years. Additionally, patients were required to have a total score ≥60 on the Liebowitz Social Anxiety Scale – Japanese Version (LSAS-J)[17] and ≥4 on the Clinical Global Impression – Severity Scale (CGI-S) and to exhibit fear/anxiety or avoidance traits in at least four items of the LSAS-J, of which ≥2 were social interaction items at screening and baseline visits. Patients with a total score ≥15 on the Montgomery Åsberg Depression Rating Scale[18] were excluded from the study.

Dosing method

The study comprised a 1-week screening period, 52 weeks of treatment, and a 2-week follow-up period. ESC 10 mg tablets were administered orally once daily during the treatment period. After the first week of this study, during which patients received 10 mg/day of ESC, the dosage was flexible (10 or 20 mg/day) and could be increased, maintained, or decreased at the discretion of the investigator.

Endpoints and evaluation method

The following six indicators were used for safety evaluation: adverse events (AEs); clinical laboratory values (hematology, biochemistry, and urinalysis); vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate); body weight; standard 12-lead electrocardiogram (ECG); and the Columbia Suicide Severity Rating Scale.[19] Clinical laboratory values and standard 12-lead ECG parameters were measured by the central laboratory.

For efficacy evaluation, the LSAS-J and the Japanese version of the Sheehan Disability Scale (SDISS)[20] were assessed at baseline visits, at weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, and 52 or at discontinuation of treatment. The CGI was assessed at baseline visits, at weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52, or at discontinuation of treatment. Social Anxiety/*Taijin-Kyofu* Scale (SATS)[5] was assessed at baseline visits, at weeks 12, 24, and 52, or at discontinuation of treatment.

Of these, the LSAS-J, CGI-S, and Clinical Global Impression – Improvement Scale (CGI-I) are commonly used in clinical studies targeting patients with SAD. The LSAS is an outcome measure for SAD that comprises two subscales, fear/anxiety and avoidance, each consisting of 24 items. The Japanese version, the LSAS-J, is used in Japan. The SATS is a structured interview-style outcome measure comprising three subscales: fear/anxiety, avoidance behaviors, and c-TK's cognitive symptoms (thinking that one's body odor, eye expression, physical appearance, or facial expression

makes other people feel unpleasant and knowing, based on how others behave, that these shortcomings exist), each consisting of four items (each item ranges from 0 to 4, with a maximum total of 16 per subscale, for a total maximum of 48), which are used to evaluate both SAD and TK. SDISS is a patient-reported evaluation of functional changes in daily life. Raters received training in advance on the LSAS-J and SATS to standardize assessments.

In this study, the CYP2C19 genotype for each patient was determined, and safety and effectiveness were stratified by CYP2C19 genotype.

Analysis

Analysis sets

The safety analysis set comprised patients administered ESC at least once. The efficacy analysis set comprised patients in the safety analysis set with at least one valid postbaseline LSAS-J assessment (full analysis set [FAS]).

Analytical methods

For safety, summary statistics were calculated for AEs and adverse drug reactions (ADRs) (ADRs = AEs where a causal relationship to the investigational drug could not be ruled out) incidences, clinical laboratory test values, vital signs, body weight, ECG, and Columbia Suicide Severity Rating Scale. The *Medical Dictionary for Regulatory Activities* Ver 16.0 was used for AE preferred terms. For efficacy, summary statistics were calculated for remission rates based on LSAS-J total scores (percentage of patients with LSAS-J total score ≤30), response rates based on LSAS-J total scores (percentage of patients with a decrease ≥30% from baseline in LSAS-J total score) and CGI-I (CGI-I ≤2), and changes in the LSAS-J total score, SATS total score, CGI-S and SDISS total score, and CGI-I.

Results

Patient background

Figure 1 shows the breakdown of patients included in this study. All 158 patients were included in both efficacy and safety analysis sets. The 52-week treatment period was completed by 81.0% (128/158) of patients. The overall withdrawal rate was 19.0% (30/158). AEs (10.8%, 17/158) were the most common reason for withdrawal, followed by withdrawal of consent (8.2%, n=13).

Table 1 shows demographic and other baseline characteristics of the study population. There was an equal distribution of males and females. Age (mean ± SD) was 33.3±10.8 years. The percentage of patients who were CYP2C19 PMs was 13.3% (21/158).

All patients received 10 mg/day ESC for the first week and 31.6% (n=50) stayed on 10 mg/day throughout the entire treatment period. Of the 108 patients (68.4%) who increased their dose to 20 mg/day, 89 patients (56.3%) stayed on this dose. The final daily dose of ESC was 10 mg for 66 patients (41.8%) and 20 mg for 92 patients (58.2%). Over 83.5% of patients (n=132) were exposed to ESC for more than 36 weeks. Participating patients were exposed to ESC for 311±111 days (mean ± SD). Treatment compliance, as measured by pill counts, was ≥75% for all but one patient.

Safety

Adverse events

The incidence of AEs was 82.9% (131/158). Median time to onset of AEs with an incidence of ≥2% was 5.5 days and

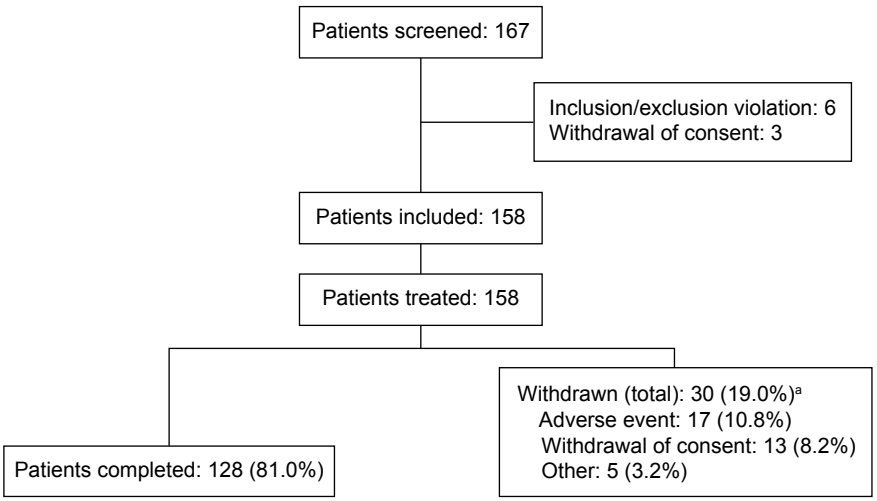

Figure 1 Flow chart of patient disposition.
Note: [a]Multiple answers may be given for reason for withdrawal.

Table 1 Demographic and other baseline characteristics (APTS, n=158)

Item	Category	Total (158 patients)
Sex		
Number of patients (%)	Male	79 (50.0)
	Female	79 (50.0)
Age (years)		
Mean ± SD		33.3±10.8
Body weight (kg)		
Mean ± SD		60.1±13.0
BMI (kg/m^2)		
Mean ± SD		22.2±4.0
CYP2C19 genotype		
Number of patients (%)	EM	137 (86.7)
	PM	21 (13.3)
Age at SAD onset (years)		
Mean ± SD		19.0±9.7
Duration of SAD (years)		
Mean ± SD		14.3±12.0
Total LSAS-J score		
Mean ± SD		95.3±19.5
Median		94.0
Minimum–maximum		60–144
Total SATS score		
Mean ± SD		23.7±6.9
Median		22.5
Minimum–maximum		11–42
CGI-S		
Mean ± SD		4.9±0.9
Median		5.0
Minimum–maximum		4–7
Total SDISS score		
Mean ± SD		11.1±6.6
Median		11.0
Minimum–maximum		0–30
Total MADRS score		
Mean ± SD		4.0±4.0
Median		3.0
Minimum–maximum		0–14

Abbreviations: APTS, all-patients-treated set; BMI, body mass index; CGI-S, Clinical Global Impression – Severity Scale; CYP, cytochrome P450; EM, extensive metabolizer; LSAS-J, Liebowitz Social Anxiety Scale – Japanese Version; MADRS, Montgomery Åsberg Depression Rating Scale; PM, poor metabolizer; SAD, social anxiety disorder; SATS, Social Anxiety/*Taijin-Kyofu* Scale; SD, standard deviation; SDISS, the Japanese version of Sheehan Disability Scale.

median duration was 11 days, that is, occurring within the first 1–2 weeks and transient.

The incidence of ADRs was 57.6% (91/158). All ADRs were either mild or moderate in severity; Table 2 shows the ADRs with an incidence ≥2%. The most common (incidence ≥10%) were somnolence and nausea. By time of onset (12-week intervals), the incidence of ADRs was highest in the period up until the end of week 12 (52.5%) and decreased subsequently from 10.6% to 4.5% from week 13 through 48. In all periods after week 13, the incidence of individual ADRs did not increase by ≥5% after week 12. The proportion of

Table 2 Adverse drug reactions by period of onset (incidence of ≥2% in treatment period)

Preferred term[a]	Adverse drug reactions											
	Overall		Until week 12		Weeks 13–24		Weeks 25–36		Weeks 37–48		Week 49 onwards	
	(158 patients)		(158 patients)		(141 patients)		(137 patients)		(133 patients)		(128 patients)	
	(79 males/79 females)		(79 males/79 females)		(72 males/69 females)		(69 males/68 females)		(67 males/66 females)		(65 males/63 females)	
	Number of patients	Incidence (%)	Number of patients	Incidence (%)	Number of patients	Incidence (%)	Number of patients	Incidence (%)	Number of patients	Incidence (%)	Number of patients	Incidence (%)
Overall	91	(57.6)	83	(52.5)	15	(10.6)	8	(5.8)	6	(4.5)	4	(3.1)
Somnolence	39	(24.7)	34	(21.5)	5	(3.5)	0		0		0	
Nausea	30	(19.0)	29	(18.4)	3	(2.1)	0		0		0	
Headache	8	(5.1)	5	(3.2)	1	(0.7)	2	(1.5)	1	(0.8)	1	(0.8)
Malaise	8	(5.1)	8	(5.1)	0		0		0		0	
Diarrhea	7	(4.4)	5	(3.2)	1	(0.7)	0		1	(0.8)	0	
Abdominal discomfort	6	(3.8)	5	(3.2)	1	(0.7)	0		1	(0.8)	0	
Abdominal pain upper	6	(3.8)	5	(3.2)	1	(0.7)	0		1	(0.8)	0	
Ejaculation disorder[b]	3	(3.8)	3	(3.8)	0		0		0		0	
Thirst	6	(3.8)	6	(3.8)	1	(0.7)	0		0		0	
Insomnia	4	(2.5)	4	(2.5)	0		0		0		0	
Initial insomnia	4	(2.5)	4	(2.5)	0		0		0		0	

Notes: [a]Dictionary: MedDRA Ver.16.0. [b]Male subjects only.
Abbreviation: MedDRA, *Medical Dictionary for Regulatory Activities*.

patients reporting ADRs by CYP2C19 genotype was 58.4% (80/137) in EMs and 52.4% (11/21) in PMs.

Serious AEs and AEs leading to discontinuation

Two patients reported serious AEs (1.3%), both during the treatment period: deep vein thrombosis and anal fissure. Deep vein thrombosis was the only severe event that occurred in this study. Neither of these events was considered by the investigator to be treatment-related. No deaths occurred in this study. No women became pregnant during this study. In this study, the incidence of AEs leading to discontinuation of treatment was 11.4% (18/158), most of which (13/18) occurred by week 12.

Other evaluation indicators

Based on the Columbia Suicide Severity Rating Scale, suicidal behavior was not detected in any patients at the start of treatment. Suicidal ideation was exacerbated from the start of treatment in 6.3% (10/158) patients; among them, seven patients were not judged to have suicide-related AEs, and three patients (five cases) were judged to have either mild or moderate AEs ("suicidal ideation") and eventually recovered. Of these five events, one was considered treatment-related by the investigator.

There were no clinically significant safety findings regarding changes in mean values of vital signs or clinical laboratory values. All mean clinical safety laboratory values were within reference ranges.

The weight increase (mean ± standard deviation [SD]) from baseline to last assessment was 1.9±3.6 kg (n=158). Weight increase was reported as an AE by three patients (1.9%, three cases). All three AEs were considered treatment-related by the investigator. One patient withdrew due to weight increase. Weight and body mass index increased from 59.5 kg and 25.4 kg/m^2 at baseline to 64.2 kg and 27.4 kg/m^2 at withdrawal (219 days after the start of treatment).

There were no clinically significant changes in the mean values of ECG parameters. The changes (mean ± SD) from baseline to last assessment of treatment in RR, PR, QRS, and Fridericia's corrected QT interval were 35.0±123.5, 0.1±12.7, 2.1±6.4, and 5.4±15.2 ms, respectively. The change (mean ± SD) from baseline to last assessment of treatment in the Fridericia's corrected QT interval was 2.4±12.0 ms (n=67) for the 10 mg dose and 7.7±16.9 ms (n=91) for the 20 mg dose. No patients had a QTcF interval >500 ms during treatment. Ten patients (6.3%) had a change from baseline to last assessment >30 ms and one patient had a change >60 ms (68 ms at week 52 and a QTcF of 469 ms).

By CYP2C19 genotype, the changes (mean ± SD) from baseline to end of treatment in the QTcF interval were 5.7±15.1 ms (n=137) in EMs and 4.0±16.3 ms (n=21) in PMs.

Effectiveness

Table 3 shows the efficacy outcomes.

LSAS-J

The LSAS-J total score (mean ± SD) decreased from 95.3±19.5 at baseline to 49.9±28.0 (observed cases [OC], FAS) at week 52 and 56.3±30.8 at last assessment (last observation carried forward, FAS).

Figure 2 shows the change in LSAS-J total score (mean ± SD) by visit. The change in LSAS-J total score (mean ± SD) from baseline was −26.6±21.5 at week 12 (n=141), −35.6±27.2 at week 24 (n=138), and −44.8±28.8 at week 52 (n=126) (OC, FAS).

Response rates based on ≥30% improvement in LSAS-J total score were 39.0% (55/141) at week 12, 55.8% (77/138) at week 24, and 69.0% (87/126) at week 52 (OC, FAS).

Remission rates based on LSAS-J total score ≤30 were 5.0% (7/141) at week 12; 18.1% (25/138) at week 24, and 27.0% (34/126) at week 52 (OC, FAS).

By CYP2C19 genotype, completion rates were 82.5% (113/137) in EMs versus 71.4% (15/21) in PMs. Response rates were 69.4% (77/111) in EMs and 66.7% (10/15) in PMs (OC, FAS). Remission rates at week 52, based on LSAS-J total score, were 27.9% (31/111) in EMs and 20.0% (3/15) in PMs (OC, FAS). Changes in LSAS-J total score (mean ± SD) were −45.1±28.5 (n=111) in EMs and −42.5±31.9 (n=15) in PMs (OC, FAS).

SATS

Change in SATS total score (mean ± SD) from baseline was −5.4±5.7 at week 12 (n=141), −7.7±6.7 at week 24 (n=138), and −11.2±7.6 at week 52 (n=126) (OC, FAS). Of 158 patients, 66 (41.8%) had SATS cognitive symptoms. Their disposition was as follows: 15 with "unpleasant body odor", ten with "inadequate eye expression", ten with "stiff facial expression", four with "perceived physical defects", and eight with "other;" 19 patients had multiple symptoms. For patients with c-TK's cognitive symptoms, changes in the SATS total score (mean ± SD) were −5.6±6.5 at week 12, −7.8±7.6 at week 24, and −12.0±9.2 at week 52 (Table 3). Additionally, 52 weeks of treatment with ESC resulted in a decrease in total scores in each of the fear/anxiety, avoidance behavior, and cognitive symptom subscales.

Table 3 Summary of efficacy evaluation (FAS)

	Baseline (158 patients)	Week 12 (141 patients)	Week 24 (138 patients)	Week 52 (126 patients)
LSAS-J total score	95.3±19.5	69.0±25.1	59.9±28.7	49.9±28.0
Change	–	–26.6±21.5	–35.6±27.2	–44.8±28.8
SATS total score	23.7±6.9	18.3±8.0	15.9±8.9	12.5±8.7
Change	–	–5.4±5.7	–7.7±6.7	–11.2±7.6
SATS total score (no cognitive symptoms)[a]	20.6±5.0	15.6±6.8	13.1±7.3	10.0±6.6
Change	–	–5.3±5.0	–7.7±6.2	–10.7±6.2
SATS total score (with cognitive symptoms)[b]	27.9±6.9	22.1±8.0	20.1±9.6	16.0±10.1
Change	–	–5.6±6.5	–7.8±7.6	–12.0±9.2
CGI-S	4.9±0.9	3.8±1.0	3.3±1.1	2.7±1.1
Change	–	–1.1±1.1	–1.6±1.3	–2.2±1.3
CGI-I	–	2.8±1.0	2.4±1.0	1.9±0.9
SDISS (work/school)	4.5±2.6	3.1±2.4	2.8±2.4	2.2±2.2
Change	–	–1.3±2.3	–1.6±2.6	–2.2±2.6
SDISS (social life)	4.0±2.5	2.8±2.1	2.6±2.2	2.0±2.0
Change	–	–1.1±2.1	–1.3±2.4	–1.9±2.4
SDISS (communication and role at home)	2.6±2.6	1.9±2.1	1.7±2.1	1.6±1.9
Change	–	–0.6±1.9	–0.8±2.3	–0.9±2.2

Notes: Data presented as mean ± SD. [a]Baseline: 92 patients, week 12: 83 patients, week 24: 82 patients, week 52: 74 patients. [b]Baseline: 66 patients, week 12: 58 patients, week 24: 56 patients, week 52: 52 patients.

Abbreviations: CGI-I, Clinical Global Impression – Improvement Scale; CGI-S, Clinical Global Impression – Severity Scale; FAS, full analysis set; LSAS-J, Liebowitz Social Anxiety Scale – Japanese Version; SATS, Social Anxiety/*Taijin-Kyofu* Scale; SD, standard deviation; SDISS, the Japanese version of Sheehan Disability Scale.

CGI

Analysis of CGI-S scores supported the clinical relevance of these long-term effectiveness results. CGI-S scores (mean ± SD) decreased throughout the study from 4.9±0.9 at baseline to 2.7±1.1 at week 52 (OC, FAS). Change in CGI-S (mean ± SD) from baseline was −1.1±1.1 at week 12 (n=141), −1.6±1.3 at week 24 (n=138), and −2.2±1.3 at week 52 (n=126) (OC, FAS).

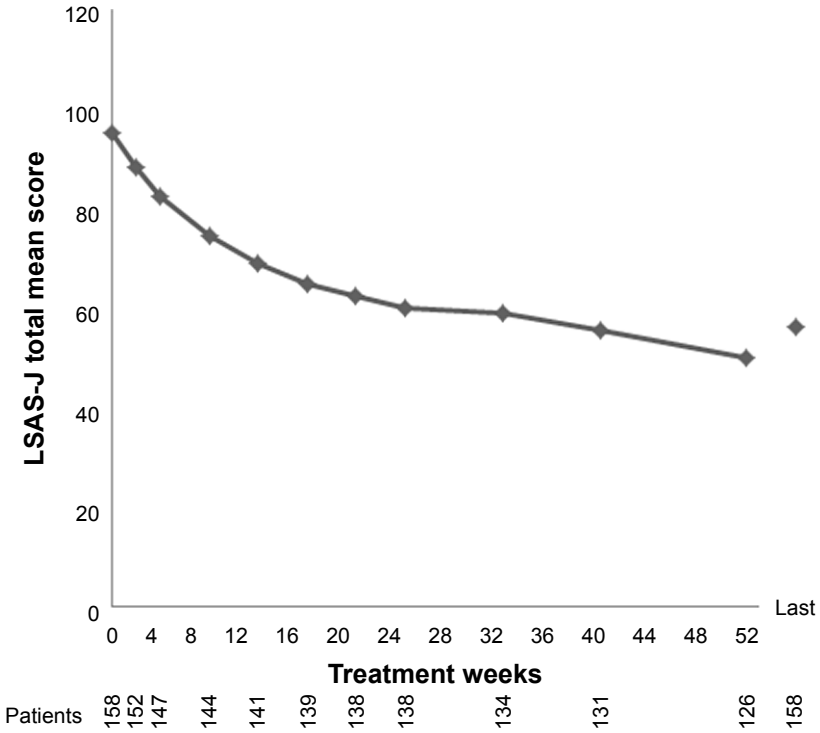

Figure 2 Estimated change in the Japanese version of the LSAS-J total scores from baseline to week 52 (FAS, OC by visit) and FAS, LOCF at last assessment.

Note: Patient numbers at each visit are shown below the *x*-axis.

Abbreviations: FAS, full-analysis set; LOCF, last observation carried forward; LSAS-J, Liebowitz Social Anxiety Scale – Japanese Version; OC, observed cases.

Patients who did not achieve sufficient efficacy with 10 mg/day ESC (based on the CGI-S) had the dose increased to and maintained at 20 mg/day ESC until the end of the treatment period. Patients were classified as improved (≥1 decrease in CGI-S), unchanged, or exacerbated (≥1 increase in CGI-S). There were 78.7% (70/89) improved patients, 19.1% (17/89) unchanged patients, and 2.2% (2/89) exacerbated patients.

CGI-I scores (mean ± SD) decreased throughout the study from 3.6±0.6 at week 2 to 1.9±0.9 at week 52 (OC, FAS). Response rates based on the percentage of patients with CGI-I ≤2 were 36.2% (51/141) at week 12; 52.2% (72/138) at week 24; and 73.0% (92/126) at week 52 (OC, FAS).

SDISS

Changes in SDISS (work/school) score (mean ± SD) from baseline were −1.3±2.3 (n=141) at week 12, −1.6±2.6 (n=138) at week 24, and −2.2±2.6 (n=126) at week 52 (OC, FAS). The corresponding changes in SDISS (social life) score (mean ± SD) from baseline were −1.1±2.1, −1.3±2.4, and −1.9±2.4, respectively (OC, FAS). The corresponding changes in SDISS (communication and role at home) score (mean ± SD) from baseline were −0.6±1.9, −0.8±2.3, and −0.9±2.2, respectively (OC, FAS).

Montgomery Åsberg Depression Rating Scale

The Montgomery Åsberg Depression Rating Scale total score (mean ± SD) improved from 4.0±4.0 at baseline to 2.8±4.0 (week 12), 2.4±3.3 (week 24), and 2.1±4.2 (week 52) (OC, FAS). Changes in Montgomery Åsberg Depression Rating Scale total score (mean ± SD) from baseline were −1.0±3.3 (n=141) at week 12, −1.4±3.1 (n=138) at week 24, and −1.9±4.5 (n=126) at week 52 (OC, FAS).

Discussion

This is the first 52-week clinical study of ESC in SAD. The primary objective was to investigate the safety and tolerability of ESC in Japanese patients with SAD, and investigation of effectiveness was planned as a secondary objective. The completion rate of 81.0% was high for a study of this duration. The rate of withdrawal due to AEs in this study was 10.8% (17/158), similar to that reported in a long-term safety extension study with ESC (8.8%) in patients with major depressive disorder in Europe/Canada.[21]

ADRs had an incidence of 57.6% (91/158) and all were either mild or moderate; the most common were somnolence and nausea. There were no deaths and the incidence of serious AEs was 1.3% (2/158). No ADRs had an increase >5% in incidence during the subsequent weeks of long-term ESC administration, compared with the period until week 12. Most AEs were transient and occurred within the first week, with a median time of 5.5 days and a duration of 11 days. Most AEs leading to discontinuation of treatment occurred before week 12, were either mild or moderate in severity, and eventually resolved. Suicidal ideation occurred in three patients; all these events were mild or moderate in severity, and all resolved.

ESC was safe and well tolerated in long-term treatment of Japanese patients with SAD with the majority of AEs being nonsevere and transient, with no new AEs that had not been seen during acute treatment.

In another randomized study comparing ESC and placebo in the treatment of patients with SAD for 24 weeks, the proportion of patients with AEs was 68.9% for 5 mg/day ESC, 72.5% for 10 mg/day ESC, and 78.2% for 20 mg/day ESC; most of these AEs were either mild or moderate.[12] These results were similar to those of the present study in Japan (74.7% at week 24). Additionally, the most frequent AEs (reported by ≥10% of patients and more than twice that in the placebo group) occurring in the 10–20 mg groups were nausea, increased sweating, diarrhea, somnolence, and ejaculation disorder,[12] and so no major differences were found between studies inside and outside Japan.

ESC is metabolized primarily by CYP2C19, and it is known that around 20% of Japanese are CYP2C19 PMs. The percentage of CYP2C19 PMs was 13.3% in this study. The $AUC_{0-\infty}$ of ESC in plasma found in PM patients was about twice that in EM patients. Incidences of ADRs were similar in CYP2C19 EMs and PMs. No major differences were found between EMs and PMs in the effect on QTcF interval.

The mean weight gain was 1.9 kg from the start of the lead-in study and one patient withdrew from the study due to weight increase.

LSAS-J, the efficacy endpoint in this study, revealed an improving tendency over time by week 52. The LSAS-J response rate (≥30% improvement in LSAS-J) was 69%, CGI-I response rate (CGI-I ≤2) was 73%, and LSAS-J remission rate (LSAS-J ≤30) was 27% at week 52. Trends for all SDISS subscores were similar, suggesting that efficacy was maintained, and quality of life may improve with long-term ESC administration. Furthermore, the ≥70% patients whose dose was increased and maintained at 20 mg/day improved their CGI-S score, suggesting that increasing the ESC dose to 20 mg/day in patients who did not improve on 10 mg/day ESC may be useful.

In this study, SATS was used as an efficacy endpoint to evaluate patients with SAD from a TK perspective. Patients believed to have c-TK (patients diagnosed with cognitive symptoms in SATS) comprised 41.8% of the study population (66/158). On each of the fear/anxiety, avoidance behavior, and c-TK's cognitive symptom subscales, use of ESC for 52 weeks resulted in decreased total scores, suggesting that administering ESC may also result in improved c-TK symptoms. Because the *Diagnostic and Statistical Manual of Mental Disorders-5* notes that c-TK may also exist outside Asia, investigating the therapeutic efficacy of drugs in TK outside Japan may prove necessary in the future.

There are several notable limitations regarding this study. This study was an open-label, uncontrolled study conducted only in Japan, limiting the generalizability of findings. The study patients are a specific population defined by the inclusion and exclusion criteria.

In conclusion, this first 52-week clinical study showed that ESC 10–20 mg/day is safe, well tolerated, and effective in Japanese patients with SAD.

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Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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