Current Medical Research and Opinion

ISSN: 0300-7995 (Print) 1473-4877 (Online) Journal homepage: http://www.tandfonline.com/loi/icmo20

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To cite this article: Satoshi Asakura, Taiji Hayano, Atsushi Hagino & Tsukasa Koyama (2016): A randomized, double-blind, placebo-controlled study of escitalopram in patients with social anxiety disorder in Japan, Current Medical Research and Opinion, DOI: 10.1185/03007995.2016.1146663

To link to this article: http://dx.doi.org/10.1185/03007995.2016.1146663

Accepted author version posted online: 25 Jan 2016.
Published online: 05 Feb 2016.

CURRENT MEDICAL RESEARCH AND OPINION, 2016
http://dx.doi.org/10.1185/03007995.2016.1146663
Article FT-0561.R1/1146663

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ORIGINAL ARTICLE

A randomized, double-blind, placebo-controlled study of escitalopram in patients with social anxiety disorder in Japan

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ABSTRACT

Objective This randomized, double-blind placebo-controlled study compared the efficacy and tolerability of escitalopram (10 and 20 mg/day) in Japanese patients with social anxiety disorder (SAD).

Research design and methods Patients aged 18–64 years with a primary diagnosis of DSM-IV-TR defined SAD, a Liebowitz Social Anxiety Scale Japanese version (LSAS-J) total score ≥60 and a Clinical Global Impression–Severity (CGI-S) score ≥4 at baseline were randomly assigned (1:1:1) to placebo, escitalopram 10 mg or escitalopram 20 mg. The primary endpoint was change from baseline to Week 12 in the LSAS-J total score for both escitalopram 10 mg and 20 mg versus placebo (ANCOVA, FAS, LOCF), using a hierarchical testing procedure. Pre-specified secondary endpoints included LSAS-J sensitivity analyses.

Clinical trial registration This study has the www.japic.or.jp identifier: JapicCTI-121842.

Results For the primary efficacy endpoint, the difference from placebo in the LSAS-J was −3.9 ($p = 0.089$) for escitalopram 10 mg. Since the superiority of escitalopram 10 mg over placebo was not confirmed, an analysis without multiplicity adjustment was made, which showed a difference for escitalopram 20 mg versus placebo of −9.8 ($p < 0.001$). In pre-specified sensitivity analyses, the difference versus placebo was −4.9 ($p = 0.035$) (ANCOVA, FAS, OC) and −5.0 ($p = 0.028$) (MMRM, FAS) (escitalopram 10 mg) and −10.1 ($p < 0.001$) (ANCOVA, FAS, OC) and −10.6 ($p < 0.001$) (MMRM, FAS) (escitalopram 20 mg). Common adverse events (incidence ≥5% and significantly different from placebo) were somnolence, nausea and ejaculation disorder.

Conclusion Escitalopram was efficacious, safe and well tolerated by patients with SAD in Japan. Study limitations are discussed including patient characteristics.

ARTICLE HISTORY
Received 18 December 2015
Revised 15 January 2016
Accepted 20 January 2016
Published online 3 February 2016

KEYWORDS
Escitalopram; Japan; Liebowitz Social Anxiety Scale Japanese version (LSAS-J); Randomized placebo-controlled study; Social anxiety disorder (SAD)

Introduction

Escitalopram (ESC) is a selective serotonin reuptake inhibitor (SSRI). As of the end of December 2014, ESC had been approved in 100 countries. Depending on the specific country or region, ESC is approved for indications that include major depressive disorder, panic disorder, social anxiety disorder (SAD), generalized anxiety disorder, obsessive–compulsive disorder, and premenstrual dysphoric disorder.

SAD is a psychiatric disorder characterized by feelings of fear and severe strain stemming from interpersonal communication, with associated symptoms such as tremor, flushing, palpitations, and sweating[1]. Anxiety disorders, including SAD, are risk factors associated with suicidal ideation and attempted suicide. The associated risk is reported to increase with a concurrent incidence of a mood disorder and anxiety disorder[2]. Because SAD develops around the onset of adolescence and is more intractable than other anxiety disorders and more likely to become chronic[3,4], it is well recognized that the condition requires treatment. In addition, because patients tend to be socially isolated due to the continuous avoidance of social relationships, SAD affects patients' engagement in school, educational settings and workplaces, with subsequent negative impacts on their economic situation[3]. These effects may represent major losses not only to the patients themselves and their families, but also to society as a whole.

Treatments for SAD are broadly classified into pharmacotherapy and psychotherapy, the latter represented by psychotherapeutic interventions, including cognitive behavior therapy. First-line pharmacotherapy includes SSRIs or serotonin noradrenaline reuptake inhibitors (SNRIs)[1,5].

Placebo-controlled studies conducted in Europe, Canada and South Africa support the efficacy of ESC in the treatment of SAD[6]. The 12 month prevalence of SAD is 2.3% in Japan[7], where only paroxetine and fluvoxamine have been approved for the treatment of SAD.

The aim of this clinical study was to investigate the efficacy, safety, and tolerability of two fixed doses (10 and 20 mg/day) of ESC versus those of placebo after 12 weeks of treatment in Japanese adult patients with SAD.

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Patients and methods

Study design

This multicenter, randomized, double-blind, parallel-group, fixed-dose, placebo-controlled study included 588 randomized patients recruited from 86 medical institutions in Japan from June 2012 to March 2014. All participating medical institutions received approval to conduct the study from their local institutional review board prior to study initiation. All study procedures were conducted in compliance with the *Declaration of Helsinki* and the Ministerial Ordinance on *Good Clinical Practice*. In addition, the study investigator obtained written informed consent from all patients prior to their participation in the study.

After a 1 week screening period, eligible patients were randomly assigned (1:1:1) to placebo, ESC 10 mg/day or ESC 20 mg/day for 12 weeks of double-blind treatment. For the ESC 20 mg group, patients were treated at an initial dose of 10 mg/day for the first week, and then there was a mandatory increase to 20 mg/day. Patients were seen at baseline and at Weeks 1, 2, 4, 6, 8 and 12. Patients who were withdrawn were seen as soon as possible after withdrawal. A safety follow-up contact was scheduled for 2 weeks after completion of the treatment period or after withdrawal from the study. Study medication was given as placebo or ESC tablets of identical appearance. Patients were instructed to take two tablets per day, orally, after supper in the evening.

Main entry criteria

Eligible patients of either sex were aged $\geq$18 and $\leq$64 years, with a primary diagnosis of SAD according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR). Patients were diagnosed using the Mini-International Neuropsychiatric Interview (MINI; Japanese version 5.0.0). In addition, patients were required to have a total score $\geq$60 on the Japanese version of the Liebowitz Social Anxiety Scale (LSAS-J) and $\geq$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 $\geq$2 were social interaction items at screening and baseline visits. Patients who met any of the following criteria were excluded from the study: diagnosis of schizophrenia or another psychotic disorder; delirium; dementia; amnestic disorder or another cognitive disorder; bipolar disorder; obsessive–compulsive disorder; panic disorder; specific phobias; body dysmorphic disorder; eating disorder; substance abuse or substance dependence (excluding nicotine and caffeine); pervasive developmental disorder on Axis I of the DSM-IV-TR; diagnosis with group A or group B personality disorder and mental retardation on Axis II of the DSM-IV-TR; history of schizophrenia or another psychotic disorder or bipolar disorder on Axis I of the DSM-IV-TR; primary diagnosis with Axis I disorder other than SAD according to the DSM-IV-TR within 24 weeks of the study; a total score $\geq$15 on the Montgomery–Åsberg Depression Rating Scale (MADRS); history or complication of convulsive disorder such as epilepsy (excluding febrile seizure in childhood); patients with congenital long QT interval syndrome, bleeding tendency, or hemorrhagic diathesis; patients at significant risk of suicide as clinically judged by the investigator, or patients meeting the criteria of any of C4 through C6 in 'C. Suicidality' of the MINI or having a score $\geq$5 on Item 10 of the MADRS ('suicidal thoughts') or with suicidal behavior according to the Columbia Suicide Severity Rating Scale Questionnaire (C-SSRS); patients who were pregnant or breastfeeding, who might be pregnant, or who wanted to get pregnant during the term of the study; and patients otherwise judged by investigators to be unsuitable for participation in this clinical study.

Efficacy rating

The effect of ESC versus placebo after 12 weeks of treatment was assessed using the LSAS-J total score. All raters underwent training in the LSAS-J, in order to maximize inter-rater reliability. Only trained raters (all of whom were either psychiatrists or psychologists) were allowed to rate patients.

Allocation to treatment

At each site, sequentially enrolled patients were assigned the lowest randomization number available in blocks of 6. Each patient was assigned a randomization number according to a randomization list that was computer generated by the study medication allocation manager. All investigators, trial personnel and patients were blinded to treatment assignment for the duration of the study. The randomization code was not broken for any patients during treatment.

Analysis sets

Safety analyses were based on the all-patients-treated set (APTS), comprising all randomized patients who took at least one dose of study medication. Efficacy analyses were based on the modified intent-to-treat set – the full-analysis set (FAS), comprising all patients in the APTS who had a valid baseline assessment and at least one valid post-baseline assessment of the primary efficacy variable (LSAS-J total score). Statistical analyses were performed using SAS 9.2 and the level of statistical significance was defined as $p < 0.05$ (two-sided).

Power and sample size calculations

Based on a previous ESC study in SAD[8], with a mean difference to placebo of 7.27 on the change from baseline in the LSAS-J total score at Week 12 and a standard deviation of 24.85, calculations showed that with a power of $\geq$80%, a total of 555 patients should be randomized to detect superiority of ESC to placebo, using a 5% level of significance and a standard *t*-test.

Analysis of the primary efficacy endpoint

The prospectively defined primary efficacy analysis was an analysis of covariance (ANCOVA) of the change from baseline

in the LSAS-J total score at Week 12 (FAS), with treatment as a fixed factor and the baseline LSAS-J total score as a covariate, using last observation carried forward (LOCF). Sensitivity analyses to the primary efficacy analysis were performed using ANCOVA based on data from observed cases (OCs), and mixed model repeated measures (MMRM). To control for a two-sided type I error in the primary efficacy endpoint, a closed testing procedure was adopted in which ESC 10 mg/day versus placebo was tested first and then ESC 20 mg/day versus placebo. Once an endpoint was non-significant, the formal testing procedure was stopped. For endpoints that occurred after the pre-specified statistical testing procedure was stopped or that were outside the testing procedure, nominal *p*-values with no adjustment for multiplicity are reported. Three *post-hoc* analyses using ANCOVA (FAS, LOCF) were also made excluding patients who discontinued within 1 week after treatment initiation; patients with non-severe SAD; and patients with severe SAD.

Analysis of secondary efficacy endpoints

The following secondary analyses were prospectively defined: the change from baseline in the LSAS-J total score at other visits, the change from baseline to Week 12 in LSAS-J subscale scores and CGI-S scores, and CGI-I scores, LSAS-J response (≥30% decrease from baseline) and CGI-I response (CGI-I score ≤2) at Week 12.

Response rates were analyzed using Fisher's exact test, and CGI-I scores were analyzed by an ANOVA. Changes from baseline were analyzed in a manner similar to the primary analysis of the primary endpoint.

Safety assessments

All treatment-emergent adverse events (TEAEs) either observed by the investigator or reported spontaneously by the patient were recorded. Qualified personnel coded TEAEs using the preferred term according to the Medical Dictionary for Regulatory Activities/Japanese (MedDRA/J), Version 16.0. The incidence of individual TEAEs was compared between treatment groups using Fisher's exact test. Clinical safety laboratory tests, vital signs, weight, BMI, ECGs, and physical examination findings were also evaluated. The Wilcoxon two-sample text was used to compare the change in the Fridericia's corrected QT interval (QTcF) between the treatment groups. A safety follow-up contact was scheduled for 2 weeks after completion of the study or after withdrawal from the study. The C-SSRS was used to assess suicide risk in patients at screening, baseline, and Weeks 1, 2, 4, 6, 8 and 12.

Results

Patient baseline characteristics

The APTS consisted of 587 patients ($n = 196$ for placebo, $n = 198$ for ESC 10 mg, and $n = 193$ for ESC 20 mg) after the exclusion of one patient who did not take any study medication (Figure 1). Patients had a mean age of about 33 years, and approximately 56% were women. There were no apparent clinically relevant differences at baseline between treatment groups in demographic or baseline clinical characteristics (Table 1). The full-analysis set (FAS) comprised 587 patients.

The mean baseline LSAS-J total score was 94.4 ± 18.1, and the mean age of onset was 19 years (median of 17 years, range 5–61 years) before enrolment. The mean baseline MADRS total score was 3.7 ± 3.9.

Withdrawals from the study

The proportions of patients who discontinued from the study in the treatment period were 10.7% (21/196) in the placebo group, 10.1% (20/198) in ESC 10 mg, and 11.9% (23/194) in ESC 20 mg (Figure 1). The most common reason for discontinuation in the ESC group was TEAEs: the proportions of patients who discontinued from the study because of TEAEs were 3.6% (7/196) in the placebo group, 6.6% (13/198) in ESC 10 mg, and 7.2% (14/194) in ESC 20 mg.

Efficacy

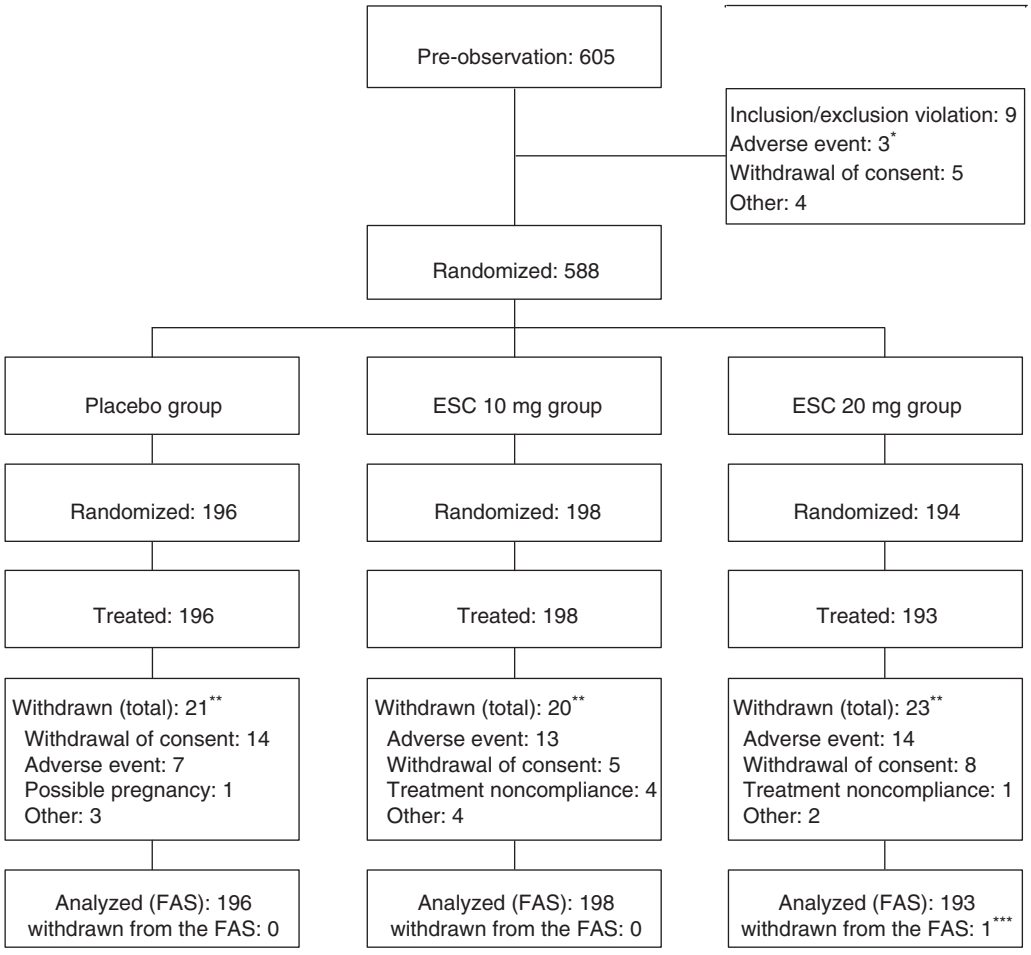
Primary endpoint

In the primary efficacy analysis, the mean change from baseline in the LSAS-J total score at Week 12 (FAS, LOCF) was −23.1 (placebo), −26.9 (ESC 10 mg) and -32.6 (ESC 20 mg). The mean difference from placebo for ESC 10 mg was −3.9 (95% CI: −8.3, 0.6) ($p = 0.089$) (Table 2). Pre-specified sensitivity analyses OCs (FAS) and MMRM (FAS) resulted in *p*-values of 0.035 and 0.028, respectively (Table 2).

Because the superiority of ESC 10 mg to placebo (FAS, LOCF) was not statistically significant, a comparison of ESC 20 mg to placebo using a closed testing procedure was not possible. However, in an analysis that did not take multiplicity into account (FAS, LOCF), the difference in the mean between placebo and ESC 20 mg was −9.8 (95% CI: −14.5, −5.2) ($p < 0.001$). The estimated change from baseline in the LSAS-J total mean score plotted by visit is shown in Figure 2.

The number of patients who discontinued within 1 week after treatment initiation was 0.5% (1/196) for placebo, 4.5% (9/198) for ESC 10 mg, and 2.6% (5/193) for ESC 20 mg, although all patients in ESC groups received ESC 10 mg/day during the first week. LSAS-J total scores measured at the withdrawal visit increased for these patients, indicating that they had discontinued treatment before a therapeutic effect had been seen. Based on this, a *post-hoc* efficacy analysis was made excluding these 15 patients. The mean difference to placebo was −5.1 (95% CI: −9.6, −0.7) ($p = 0.023$) for ESC 10 mg and −10.6 (95% CI: −15.2, −5.9) ($p < 0.001$) for ESC 20 mg (FAS, LOCF).

When stratified according to cytochrome P450 (CYP) 2C19 phenotype, the mean difference to placebo on the MADRS for poor metabolizers ($n = 113$) was +3.9 (95% CI: −7.0, 14.9) ($p = 0.477$) for ESC 10 mg and −11.4 (95% CI: −22.1, −0.7) ($p = 0.038$) for ESC 20 mg; and for extensive metabolizers ($n = 474$), the mean difference to placebo was −5.5 (95%



*The adverse events occurred during the taking of placebo.
**Multiple answers are available for reason of discontinuation.
***Patient took no study medication.

Figure 1. Flow chart of patient disposition. ESC: escitalopram, FAS: full-analysis set.

Table 1. Baseline patient characteristics (mean ± SD).

APTS	Placebo ($n = 196$)	Escitalopram 10 mg ($n = 198$)	Escitalopram 20 mg ($n = 193$)	Total ($n = 587$)
Gender (% female)	55.6	56.6	54.9	55.7
Mean weight (kg)	58.21 ± 11.79	58.45 ± 11.33	59.06 ± 13.04	58.57 ± 12.05
Mean height (cm)	163.85 ± 7.99	164.08 ± 8.39	163.96 ± 8.48	163.96 ± 8.28
BMI (kg/m^2)	21.56 ± 3.37	21.65 ± 3.50	21.86 ± 3.86	21.69 ± 3.58
Mean age, range (years)	33.0 (18–63)	33.6 (18–62)	32.5 (18–64)	33.0 (18–64)
Age at SAD onset (years)	18.8 ± 9.6	18.8 ± 9.0	18.8 ± 8.8	18.8 ± 9.1
Duration of SAD (years)	14.2 ± 10.5	14.7 ± 10.1	13.7 ± 10.6	14.2 ± 10.4
History of pharmacotherapy for SAD (%)	57.1	58.6	56.5	57.4
1 drug* (%)	21.4	30.8	27.5	26.6
2 drugs* (%)	7.7	5.1	3.1	5.3
3 drugs* (%)	3.6	2.5	3.1	3.1
4 drugs* (%)	0.5	1.0	0	0.5
CYP2C19 genotype (% EMs)	80.6	82.8	78.8	80.7
Comorbid psychiatric disorder (%)	14.3	18.2	20.2	17.5
Mean baseline LSAS-J total score	95.3 ± 18.5	94.5 ± 18.2	93.4 ± 17.8	94.4 ± 18.1
Fear/anxiety subscale	51.4 ± 9.1	51.1 ± 9.3	50.5 ± 8.9	51.0 ± 9.1
Avoidance subscale	43.9 ± 10.7	43.4 ± 10.5	42.8 ± 10.5	43.4 ± 10.5
Mean baseline MADRS total score	3.6 ± 4.0	3.6 ± 3.9	3.9 ± 3.8	3.7 ± 3.9
Mean baseline CGI-S	4.8 ± 0.8	4.8 ± 0.9	4.9 ± 0.8	4.8 ± 0.8

*Number of selective serotonin reuptake inhibitors (SSRIs) or serotonin noradrenaline reuptake inhibitors (SNRIs).
BMI: body mass index, CGI-S: Clinical Global Impressions–Severity of Illness, CYP: cytochrome P450, EMs: extensive metabolizers, LSAS-J: Liebowitz social anxiety scale – Japanese version, MADRS: Montgomery–Åsberg Depression Rating Scale, SAD: social anxiety disorder.

Table 2. Summary of LSAS-J efficacy assessments (mean ± SD) (FAS).

Group	*N*	LSAS-J total score			Comparison with placebo	
		Baseline	Week 12	Change from baseline	Difference (95% CI)	*p*-value
ANCOVA (LOCF)[a]						
Placebo	196	95.3 ± 18.5	72.2 ± 27.4	−23.1 ± 21.4	—	
10 mg/day	198	94.5 ± 18.2	67.6 ± 29.0	−26.9 ± 23.3	−3.9 (−8.3, 0.6)	0.089
20 mg/day	193	93.4 ± 17.8	60.7 ± 28.0	−32.6 ± 25.6	−9.8 (−14.5, −5.2)	<0.001
ANCOVA (OCs)[b]						
Placebo	175	94.7 ± 18.3	69.4 ± 26.6	−25.3 ± 21.2	—	
10 mg/day	177	93.5 ± 18.1	63.4 ± 27.2	−30.1 ± 22.4	−4.9 (−9.5, −0.3)	0.035
20 mg/day	171	93.6 ± 17.8	58.4 ± 27.7	−35.2 ± 25.1	−10.1 (−15.0, −5.3)	<0.001
MMRM[b]						
Placebo	196	95.3 ± 18.5	69.4 ± 26.6	−25.3 ± 21.2	—	
10 mg/day	198	94.5 ± 18.2	63.4 ± 27.2	−30.1 ± 22.4	−5.0 (−9.5, −0.5)	0.028
20 mg/day	193	93.4 ± 17.8	58.4 ± 27.7	−35.2 ± 25.1	−10.6 (−15.4, −5.9)	<0.001
ANCOVA (LOCF) excluding patients discontinued in the first week[c]						
Placebo	195	95.2 ± 18.5	72.0 ± 27.4	−23.3 ± 21.4	—	—
10 mg/day	189	94.3 ± 18.3	66.0 ± 28.4	−28.3 ± 22.9	−5.1 (−9.6, −0.7)	0.023
20 mg/day	188	93.6 ± 17.8	60.0 ± 27.9	−33.5 ± 25.3	−10.6 (−15.2, −5.9)	<0.001

[a]Pre-specified primary endpoint.
[b]Pre-specified sensitivity analysis.
[c]*Post-hoc* analysis.
95% CI: 95% confidence interval, ANCOVA: analysis of covariance, FAS: full-analysis set, LOCF: last observation carried forward, LSAS-J: Liebowitz social anxiety scale – Japanese version, MMRM: mixed model repeated measures, OCs: observed cases.

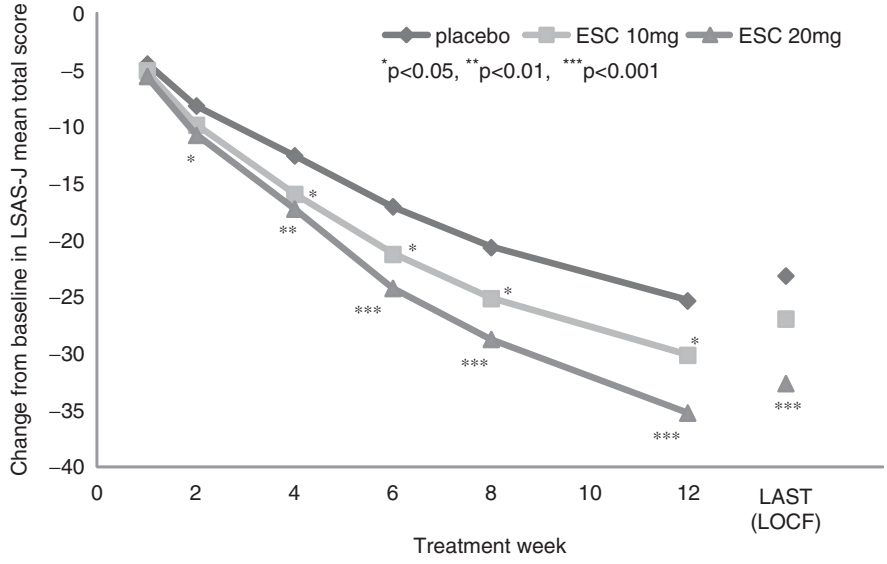


Figure 2. Estimated change in Liebowitz Social Anxiety Scale (LSAS-J) total scores from baseline to Week 12 (FAS, OCs by visit) and FAS, LOCF at Week 12. FAS: full-analysis set, LOCF: last observation carried forward, OCs: observed cases. The pre-specified primary endpoint is at Week 12 (FAS, ANCOVA, LOCF). $*p < 0.05$, $**p < 0.01$, $***p < 0.001$ *versus* placebo.

CI: −10.4, −0.7) ($p = 0.026$) for ESC 10 mg and -9.4 (95% CI: −14.6, −4.1) ($p < 0.001$) for ESC 20 mg (FAS, LOCF).

A small proportion of patients had severe SAD (17.5%), defined as a baseline LSAS-J total score ≥100 and a CGI-S score ≥6. In *post-hoc* analyses of patients with non-severe SAD ($n = 484$), the difference to placebo in the mean change from baseline in the LSAS-J total score was −5.4 (95% CI:−10.2, −0.7) ($p = 0.026$) for ESC 10 mg and −9.9 (95% CI:-14.8, −4.9) ($p < 0.001$) for ESC 20 mg. For patients with severe SAD ($n = 103$), the difference to placebo was +2.9 (95% CI:-9.1, 14.9) ($p = 0.635$) for ESC 10 mg and −9.9 (95% CI: −24.0, 4.2) ($p = 0.164$) for ESC 20 mg.

The two subscales of the LSAS-J were also analyzed by ANCOVA (FAS, LOCF). The mean difference from placebo for the LSAS-J fear/anxiety subscale total score was −2.1 (95% CI: −4.3, 0.2) ($p = 0.069$) for ESC 10 mg and −4.9 (95% CI: −7.3, −2.5) ($p < 0.001$) for ESC 20 mg (FAS, LOCF). The mean difference from placebo for the LSAS-J avoidance subscale total score was −1.8 (95% CI: −4.2, 0.5) ($p = 0.124$) for ESC 10 mg and −5.0 (95% CI: −7.4, −2.6) ($p < 0.001$) for ESC 20 mg (FAS, LOCF) (Table 3).

Secondary analyses

Mean CGI-I and CGI-S scores improved throughout the 12 week treatment period in all treatment groups. The CGI-S scores improved from baseline to Week 12 from 4.8 ± 0.8 to 3.8 ± 1.0 (placebo), from 4.8 ± 0.9 to 3.7 ± 1.3 (ESC 10 mg) and from 4.9 ± 0.8 to 3.5 ± 1.2 (ESC 20 mg). The differences to placebo were −0.1 (95% CI: -0.4, 0.1) ($p = 0.178$) (ESC

Table 3. Summary of LSAS-J subscale efficacy assessments (mean ± SD) (FAS, LOCF).

Group	*N*	LSAS-J subscale total score			Comparison with placebo	
		Baseline	Week 12	Change from baseline	Difference (95% CI)	*p*-value[a]
Fear/anxiety subscale						
Placebo	196	51.4 ± 9.1	39.9 ± 13.8	−11.5 ± 10.9	—	
10 mg/day	198	51.1 ± 9.3	37.6 ± 14.8	−13.5 ± 11.5	−2.1 (-4.3, 0.2)	0.069
20 mg/day	193	50.5 ± 8.9	34.3 ± 14.6	−16.2 ± 13.2	−4.9 (-7.3, -2.5)	<0.001
Avoidance subscale						
Placebo	196	43.9 ± 10.7	32.3 ± 14.5	−11.7 ± 11.3	—	
10 mg/day	198	43.4 ± 10.5	30.0 ± 15.2	−13.4 ± 12.5	−1.8 (-4.2, 0.5)	0.124
20 mg/day	193	42.8 ± 10.5	26.4 ± 14.5	−16.4 ± 13.1	−5.0 (-7.4, -2.6)	<0.001

[a]ANCOVA: analysis of covariance.
95% CI: 95% confidence interval, FAS: full-analysis set, LOCF: last observation carried forward, LSAS-J: Liebowitz social anxiety scale – Japanese version.

Table 4. Treatment-emergent adverse events (TEAEs) in ≥5% of patients in any treatment group in the 12 week treatment period (APTS).

Preferred Term	Placebo (*n* = 196)	Escitalopram 10 mg (*n* = 198)	Escitalopram 20 mg (*n* = 193)
Patients with TEAEs	110 (56.1%)	127 (64.1%)	126 (65.3%)
Somnolence	17 (8.7%)	36 (18.2%)*	43 (22.3%)*
Nasopharyngitis	35 (17.9%)	33 (16.7%)	32 (16.6%)
Nausea	12 (6.1%)	29 (14.6%)*	31 (16.1%)*
Abdominal discomfort	4 (2.0%)	4 (2.0%)	11 (5.7%)
Headache	15 (7.7%)	10 (5.1%)	9 (4.7%)
Ejaculation disorder (men)	0	5 (5.8%)*	2 (2.3%)

APTS: all-patients-treated set.
*$p < 0.05$ versus placebo (Fisher's exact test).

Table 5. Treatment-emergent adverse events (TEAEs) in ≥2% of patients who did not receive antidepressants in any treatment group in the follow-up period (APTS).

Preferred Term	Placebo (*n* = 113)	Escitalopram 10 mg (*n* = 114)	Escitalopram 20 mg (*n* = 112)
Patients with TEAEs	12 (10.6%)	22 (19.3%)	27 (24.1%)*
Dizziness	3 (2.7%)	7 (6.1%)	12 (10.7%)*
Nasopharyngitis	3 (2.7%)	3 (2.6%)	4 (3.6%)
Nausea	1 (0.9%)	1 (0.9%)	3 (2.7%)
Headache	5 (4.4%)	2 (1.8%)	2 (1.8%)

APTS: all-patients-treated set.
*$p < 0.05$ versus placebo (Fisher's exact test).

10 mg) and −0.4 (95% CI: −0.6, −0.2) ($p < 0.001$) (ESC 20 mg) (FAS, LOCF).

The CGI-I scores improved from baseline to Week 12 to 2.8 ± 1.1 (placebo), to 2.6 ± 1.1 (ESC 10 mg) and to 2.4 ± 1.1 (ESC 20 mg). The differences from placebo were −0.2 (95% CI: −0.4, 0.0) ($p = 0.049$) (ESC 10 mg) and −0.4 (95% CI: -0.7, -0.2) ($p < 0.001$) (ESC 20 mg) (FAS, LOCF). The CGI-I response rates at Week 12 were 37.8% (95% CI: 30.9, 44.9) (placebo), 48.0% (95% CI: 40.8, 55.2) (ESC 10 mg), and 54.9% (95% CI: 47.6, 62.1) (ESC 20 mg), The differences in the response rate from placebo were 10.2% (95% CI: 0.5, 19.9) ($p = 0.042$) (ESC 10 mg) and 17.2% (95% CI: 7.4, 26.9) (ESC 20 mg) ($p < 0.001$) (FAS, LOCF).

Safety and tolerability

During the 12 week treatment period, approximately 70% of the patients in each ESC treatment group had one or more TEAEs. The most common TEAEs reported by at least 5% of patients for ESC and significantly more frequently than placebo were somnolence, nausea and ejaculation disorder (Table 4). The majority of TEAEs were mild or moderate in severity with the proportions of patients reporting severe TEAEs being 0% (0 of 196) (placebo), 1.5% (3 of 198) (ESC 10 mg), and 1.0% (2 of 193) (ESC 20 mg). During this period, 34 patients were withdrawn due to TEAEs (Figure 1). TEAEs leading to withdrawal of ≥2 patients in either group were anxiety ($n = 2$) in placebo; headache and nausea ($n = 3$ for each), social phobia, abdominal pain upper, and dizziness ($n = 2$ for each) in ESC 10 mg; and nausea ($n = 2$) in ESC 20 mg. The proportions of patients with severe TEAEs leading to withdrawal were 1.0% (2/198) (ESC 10 mg) and 1.0% (2/193) (ESC 20 mg) and the majority resolved after treatment discontinuation.

To investigate the development of possible withdrawal syndrome during the follow-up period, TEAEs in patients who did not concomitantly use an antidepressant during the follow-up period were examined.

Patients who did not receive antidepressants in the follow-up period accounted for 113 of 196 patients in the placebo group, 114 of 198 patients in ESC 10 mg, and 112 of 193 patients in ESC 20 mg. The proportions of patients with TEAEs were 10.6% (12/113) (placebo), 19.3% (22/114) (ESC 10 mg), and 24.1% (27/112) (ESC 20 mg). Dizziness was reported by 2.7% (3/113) (placebo), 6.1% (7/114) (ESC 10 mg), and 10.7% (12/112) (ESC 20 mg) of patients during follow-up (Table 5). All of these events were mild or moderate.

In the 12 week treatment period eight serious AEs (SAEs) were reported by six patients, three patients in ESC 10 mg and three patients in ESC 20 mg. No SAE was reported by more than one patient and the types of SAEs were: convulsion, acute pyelonephritis, cervical vertebral fracture, lumbar vertebral fracture, and thoracic vertebral fracture (ESC 10 mg) and appendicitis, osteoarthritis, and diabetes mellitus (ESC 20 mg). Of the aforementioned events, the cervical vertebral fracture, lumbar vertebral fracture, and thoracic vertebral fracture in ESC 10 mg were all events that occurred in the same patient, and the patient recovered from all of these events without discontinuing from study treatment. The other events all occurred in different patients and, except for diabetes, all were alleviated or recovered with study treatment discontinuation and therapy. The patient with diabetes was still receiving pharmacotherapy 4 months after discontinuing from

study treatment, at which time the patient's condition was judged to be following the natural course of diabetes by the investigator, and follow-up was therefore concluded.

No deaths occurred in this study.

The proportions of patients who reported sexual-dysfunction-related TEAEs were 2.5% (5/198) in ESC 10 mg and 2.6% (5/193) in ESC 20 mg while none were reported in the placebo group. Ejaculation disorder (five patients) and erectile dysfunction (one patient) were reported in ESC 10 mg, and ejaculation disorder (two patients), libido decreased (two patients), and ejaculation delayed (one patient) and libido increased (one patient) were reported in ESC 20 mg. All sexual-dysfunction-related TEAEs were rated by the investigator as mild in severity.

Suicide-related TEAEs were reported by 0.5% (1 of 196 placebo patients) (suicidal ideation), 1.5% (3 of 198 ESC 10 mg patients) (2 suicidal ideation and 1 self-injurious behavior), and 0% (0 of 193 ESC 20 mg patients). Each suicide-related TEAE occurred once and there were no statistically significant differences between the placebo and ESC groups. All suicide-related TEAEs were rated by the investigator as mild or moderate in severity. Of the three patients in ESC 10 mg, one of the patients with suicidal ideation and the patient with self-injurious behavior recovered without therapy, and the other patient with suicidal ideation improved without therapy after discontinuation of the study treatment. These results were supported by the C-SSRS data.

No clinically relevant changes over time or differences between treatment groups were seen in clinical laboratory test results, vital signs, weight, or ECG parameters. Patients gained a mean of 0.24 kg and 0.29 kg (ESC 10 mg or ESC 20 mg, respectively) and 0.35 kg (placebo) compared to baseline at Week 12 or last assessment. No statistically significant differences were found between ESC 10 mg ($p = 0.325$) or ESC 20 mg ($p = 0.751$) versus placebo. The differences from placebo in the mean change from baseline in QTcF interval at the end of treatment were 3.0 ms (95% CI: 0.1 to 5.8) (ESC 10 mg) and 5.0 ms (95% CI: 2.1 to 7.8) (ESC 20 mg).

The proportions of patients with TEAEs were 52.6% (placebo), 85.3% (ESC 10 mg), and 65.9% (ESC 20 mg) for CYP2C19 poor metabolizers; and 57.0% (placebo), 59.8% (ESC 10 mg), and 65.1% (ESC 20 mg) for extensive metabolizers. The differences from placebo in the mean change from baseline to the end of treatment in the QTcF interval were 4.6 ms (ESC 10 mg) ($p = 0.241$) and 3.5 ms (ESC 20 mg) ($p = 0.282$) for CYP2C19 poor metabolizers and 2.6 ms (ESC 10 mg) ($p = 0.143$) and 5.3 ms (ESC 20 mg) ($p = 0.004$) for extensive metabolizers. The completion rate in poor metabolizers was 94.7% (36/38) (placebo), 85.3% (29/34) (ESC 10 mg), and 92.7% (38/41) (ESC 20 mg). The completion rate in extensive metabolizers was 88.0% (139/158) (placebo), 90.9% (149/164) (ESC 10 mg), and 87.5% (133/152) (ESC 20 mg).

Discussion

This is the first randomized placebo-controlled clinical study for the treatment of SAD with ESC in Japan. Apart from this study, three clinical studies of ESC have been conducted in patients with SAD in countries outside of Japan. In these studies, the short-term (12 weeks) and long-term (24 weeks) efficacy and relapse-prevention effect (24 weeks) of ESC treatment were established, and its safety and tolerability were also demonstrated[6,8,9].

The primary study endpoint in this placebo-controlled study in Japan, the change in the LSAS-J total score at Week 12, was not established for ESC 10 mg versus placebo. The primary analysis was performed on data with the missing values imputed by LOCF. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E9 guidelines[10] state that "Unfortunately, no universally applicable methods of handling missing values can be recommended. An investigation should be made concerning the sensitivity of the results of analysis to the method of handling missing values, especially if the number of missing values is substantial." Thus, we performed prospectively defined sensitivity analyses based on OCs and MMRM. The results of these sensitivity analyses demonstrated the superiority of ESC 10 mg over placebo. Since different results were obtained from the sensitivity analyses, it was considered likely that the results for the primary efficacy endpoint were affected by the handling of missing values. According to the European Medicines Agency guidelines from 2010[11], it is suggested that, in the case of diseases that tend to improve spontaneously over time (such as depression), efficacy is evaluated conservatively with data imputation by LOCF analysis if there are a large number of patients in the active treatment group who discontinue treatment at an early stage. Since SAD, like depression, also tends to improve over time, it was suggested that efficacy should be evaluated conservatively by carrying out a LOCF analysis.

The proportion of discontinued patients in each treatment group, which would affect the LOCF analysis, was investigated. Although the dose was 10 mg/day for both ESC 10 mg and ESC 20 mg through Week 1 of the treatment period, the rates of patient discontinuation within this first week of treatment were 0.5% (1 of 196 patients in placebo), 4.5% (9 of 198 patients in ESC 10 mg), and 2.6% (5 of 193 patients in ESC 20 mg); i.e., a higher rate was observed in the ESC 10 mg group. In the ESC groups, the main reason for discontinuation within the first week was TEAEs; the number of patients who discontinued due to TEAEs was eight patients in ESC 10 mg and four patients in ESC 20 mg. For the patients who discontinued treatment within Week 1 of treatment, the mean change in the LSAS-J total score at treatment discontinuation indicated a slight worsening in all treatment groups. The period for efficacy evaluation was defined as 12 weeks using the treatment algorithm of Stein *et al.*[12] and the British Association for Psychopharmacology's guidelines[13], whereas the Canadian Psychiatric Association's guidelines[1] specify that an early response to pharmacotherapy is usually observed in the first 6–8 weeks, but that it may take 12 weeks or longer for pharmacotherapy to exert its full effects in some cases. Since the primary endpoint included patients who had discontinued treatment before the first week of treatment, the efficacy of ESC 10 mg was underestimated by including the values imputed by LOCF.

When the change in the LSAS-J total score at Week 12 of treatment was analyzed, significant improvement was demonstrated for ESC 20 mg versus placebo using both the primary analysis method and the sensitivity analyses. In addition, statistically significant improvements were also demonstrated for all of the pre-defined secondary endpoints for ESC 20 mg versus placebo using the LOCF analysis.

Patients were also analyzed by baseline severity, whereby severe SAD was defined as a LSAS-J total baseline score ≥100 and a CGI-S score ≥6. Analysis demonstrated statistically significant improvement in non-severe patients taking ESC 10 mg. ESC 10 mg appeared to be an insufficient dose for patients with severe SAD, whereas ESC 20 mg was equally efficacious in both severe and non-severe patients with SAD. These findings suggest that ESC is expected to be effective for non-severe SAD patients at a dose of 10 mg/day and that a dose increase to 20 mg/day is appropriate for severe SAD patients who do not respond to ESC 10 mg/day.

In a placebo-controlled, randomized, double-blind, parallel-group, fixed-dose study in which placebo, ESC 5, 10, or 20 mg/day or paroxetine 20 mg/day was administered for 24 weeks that was conducted in countries outside of Japan in SAD (Lader *et al.*)[8], the change from treatment initiation in the LSAS total score at week 12 (LOCF, mean) was −29.5 in the placebo group, −38.7 in ESC 5 mg, −34.6 in ESC 10 mg, −39.8 in ESC 20 mg, and -39.3 in the paroxetine group. There were no major differences between the studies conducted in Japan and the studies conducted outside Japan in the differences between placebo and either ESC 10 mg or ESC 20 mg in the change in the LSAS total score at week 12.

There was no marked difference between the ESC doses in the incidence of common TEAEs during treatment, and thus no indication of any dose effect. Somnolence, nausea and ejaculation disorder were reported by a greater proportion of patients treated with ESC 10 mg and ESC 20 mg than with placebo. Almost all of the TEAEs that resulted in study treatment discontinuation in all of the ESC groups were mild or moderate, and no major differences were found among the groups in the incidences thereof.

All of the suicide-related TEAEs that occurred were mild or moderate in severity, and no major differences were found between the ESC group and the placebo group in the incidence of suicide-related TEAEs.

ESC is primarily metabolized by CYP2C19, and approximately 20% of Japanese people are CYP2C19 poor metabolizers. In this study, the percentage of CYP2C19 genotype poor metabolizers was 19.3%. Because it has been shown that the $AUC_{0-\infty}$ of plasma ESC in CYP2C19 poor metabolizers is approximately twice that of extensive metabolizers[14], the safety of ESC according to CYP2C19 genotype was examined. There were no safety or tolerability issues for poor metabolizers compared to extensive metabolizers, and this included those patients with TEAEs or QTcF interval changes. Collectively, these data demonstrate that there were no major clinical problems regarding the safety findings obtained in this study.

In a 12 week, placebo-controlled, randomized, double-blind, parallel-group, variable-dose study of ESC (10 or 20 mg/day) in patients with SAD in countries outside of Japan (Kasper *et al.*)[6], the following TEAEs occurred in ≥5% of patients in the ESC group: headache, nausea, fatigue, somnolence, diarrhea, insomnia, dizziness, rhinitis, increased sweating, ejaculation failure, and decreased libido; and in the placebo group the following TEAEs occurred in ≥5% of patients: headache, nausea, fatigue, somnolence, diarrhea, insomnia, dizziness and rhinitis. There were no major differences in the TEAEs reported by patients in the two studies. The proportions of patients who discontinued due to TEAEs in the Lader *et al.* study were 4.5% in the placebo group and 8.8% in the ESC group, and it thus appears that there were no major differences in safety or tolerability between studies conducted in Japan or other countries.

A limitation of this study is the inclusion and exclusion criteria which may limit the generalizability of the results.

Conclusions

This study demonstrated the efficacy of ESC 10 mg/day and 20 mg/day in patients with SAD in Japan, as well as the safety and good tolerability of both doses of ESC.

Transparency

Declaration of funding

Mochida Pharmaceutical Co. Ltd sponsored the study and was involved in the study design, in the collection, analysis and interpretation of data, in the writing of the report, and in the decision to submit the paper for publication.

Author contributions: All authors designed the original study and wrote the protocol. T.H. monitored study progress. A.H. undertook the statistical analysis. All authors contributed to and have approved the final manuscript.

Declaration of financial/other relationships

T.H. and A.H. have disclosed that they are employees of Mochida Pharmaceutical Co. Ltd. S.A. and T.K. have disclosed that they served as medical experts for this clinical study. The expenses in preparing this paper were met by Mochida Pharmaceutical Co. Ltd.

CMRO peer reviewers on this manuscript have received an honorarium from *CMRO* for their review work, but have no relevant financial or other relationships to disclose.

Acknowledgments

We thank the following investigators for their participation in this study: Dr. Hiroki Ishikawa, Dr. Masahiko Fujita, Dr. Kunihiko Kawamura, Dr. Kyoko Kawaharata, Dr. Kimihiro Nakajima, Dr. Takeshi Fujita, Dr. Michihiro Shimode, Dr. Motomichi Shimizu, Dr. Ken-ichi Harada, Dr. Hideo Maeda, Dr. Junko Shiraki, Dr. Keiji Kaneta, Dr. Naofumi Kusaka, Dr. Shun-ichi Munakata, Dr. Hirofumi Kanome, Dr. Yoshinori Watanabe, Dr. Masatoshi Yaginuma, Dr. Toshiaki Shichijo, Dr. Hiroshi Nagao, Dr. Masaharu Asakawa, Dr. Hisashi Miyake, Dr. Masataka Noguchi, Dr. Gaku Ishikawa, Dr. Shojiro Takahashi, Dr. Il Bong Lee, Dr. Kenji Shigemori, Dr. Satoshi Nakamura, Dr. Eiji Yoshida, Dr. Hiroko Sakamoto, Dr. Jun Matsushima, Dr. Takuji Hishinuma, Dr. Masami Tanaka, Dr. Naoki Harikae, Dr. Nobutoshi Kariya, Dr. Isao Fukunishi, Dr. Jun-ichi Aoki, Dr. Naohiro Yokoyama, Dr. Masaki Kishiro, Dr. Ken-ichi Goto, Dr. Yasutaka Tawara, Dr. Kotaro Kudo, Dr. Takashi Hayama, Dr. Hiroaki Harai, Dr. Keiichi Tanaka, Dr. Tokuji Hokuto, Dr. Yuji Ikeuchi, Dr. Kiyoshi Kohduki, Dr. Takashi Taguchi, Dr. Kenji Tatsuta, Dr. Masanori Kyo, Dr. Seigen Gon, Dr. Norihide Ensako,

Dr. Osamu Yamamoto, Dr. Seiichi Tsuji, Dr. Tokumi Fujikawa, Dr. Soichiro Hirayama, Dr. Akio Mantani, Dr. Norio Yokota, Dr. Hiroshi Yamaguchi, Dr. Masamiki Kimura, Dr. Nobuhiko Imato, Dr. Hiromitsu Kaku, Dr. Naoyuki Hamada, Dr. Kazuhide Takada, Dr. Hideyo Sugahara, Dr. Masaru Yoshimura, Dr. Junko Hatakeyama, Dr. Hikari Mizuma, Dr. Hiroaki Furui, Dr. Kaori Hamada, Dr. Masahiro Matsunaga, Dr. Tetsuya Tachiyama, Dr. Joji Kobayashi, Dr. Naoki Kojima, Dr. Hideaki Sakai, Dr. Kunio Kato, Dr. Tetsuo Abe, Dr. Masanobu Takeuchi, Dr. Taihei Fukuhara, Dr. Akihiro Kakishima, Dr. Yoko Ueda, Dr. Masashi Yoshida, Dr. Takashi Furune, Dr. Kahori Ito, and Dr. Naoshige Matsuguchi.

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