We conducted a 24-week, rater-masked, randomized trial of escitalopram (5-20 mg/day) versus paroxetine controlled release (12.5-50 mg/day) in patients with MDD (UMIN000011191). Patients with the diagnosis of moderate-to-severe MDD (a 17-item Hamilton Rating Scale for Depression [HAMD-17], with total score at baseline being ≥20) were recruited to participate in a parallel, randomized, controlled trial. The primary outcome for efficacy was an improvement in the 21-item HAMD (HAMD-21) total score at 24 weeks. The secondary outcomes were the response, remission, and discontinuation rates and the incidence of individual adverse events.

**Results:** A total of 88 patients with MDD (males, 61.4%; mean age, 40.8±13.4 years) were recruited. The discontinuation rate was 58.0% (escitalopram, 55.8%; paroxetine controlled release, 60.0%). Both escitalopram and paroxetine controlled-release treatment groups exhibited significant reduction in the HAMD-21 total score at 2, 4, 8, 12, and 24 weeks from the baseline. However, there were no significant differences in the HAMD-21 total score, response rate, remission rate, and discontinuation rate at any time point between the groups. In addition, there were no significant differences in the incidence of any individual adverse events (eg, nausea, vomiting, and somnolence) between the treatment groups.

**Conclusion:** Our results suggest that escitalopram and paroxetine controlled release had similar efficacy and safety profiles in patients with MDD. One of the primary limitations of this study is the small sample size.

**Keywords:** escitalopram, paroxetine controlled release, major depressive disorder, Hamilton Rating Scale for Depression, antidepressant

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**Introduction**

In 2009, the Meta-Analysis of New Generation Antidepressants Study reported that clinically important differences for both efficacy and acceptability exist among commonly prescribed antidepressants in favor of escitalopram and sertraline. In 2012, escitalopram was demonstrated to have the highest probability of remission and is the most effective and cost-effective pharmacological treatment in a primary care setting. Escitalopram appears to be the best first-line antidepressant for treating major depressive disorder (MDD). In contrast, in 2010, paroxetine immediate release was the best-selling antidepressant in Japan.

There were three randomized trials of escitalopram versus paroxetine immediate release in patients with MDD. Boulenger et al’s study and Kasper et al’s study reported that escitalopram is more effective and safer than paroxetine immediate release in the long-term treatment of patients with MDD. Baldwin et al reported that significantly
The primary outcome measure was the improvement of the HAMD-21 total scores at week 24. The secondary outcomes included: the HAMD-21 scores at 2, 4, 8, and
12 weeks; the HAMD-17 scores at 2, 4, 8, 12, and 24 weeks; the response rate at 2, 4, 8, 12, and 24 weeks (clinical response defined as ≥50% reduction in the HAMD-17 or -21 total score from baseline to endpoint); the remission rate at 2, 4, 8, 12, and 24 weeks (clinical remission defined as the HAMD-17 total score ≤6 or HAMD-21 total score ≤7); the discontinuation rate; and individual adverse events.

Statistical analysis
Modified intent-to-treat analysis was performed using the last observation carried forward method. Baseline continuous and categorical variables were compared between the treatment groups by an independent t-test and a chi-square test, respectively. Paired Student’s t-tests were used to assess the changes in the HAMD-21 and HAMD-17 total scores from the baseline to endpoint. The comparison between the escitalopram and paroxetine controlled-release treatment groups was made by determining the change in the HAMD-21 (or HAMD-17) total score at the endpoint (2, 4, 8, 12, and 24 weeks) from baseline, based on an analysis of covariance model using the baseline HAMD-21 (or HAMD-17) score as a covariate. We also used multiple logistic regression analyses to examine which antidepressant was associated with a higher response rate or remission rate (dependent variable: response rate [HAMD-21 or HAMD-17] or remission rate [HAMD-21 or HAMD-17]; independent variable: treatment group; and covariates: baseline HAMD-21 or HAMD-17 score, respectively). A Kaplan–Meier analysis was used to estimate the time to discontinuation for the two treatment groups, and the results were compared using a log-rank test. We also compared the change in body weight from baseline to endpoint between the escitalopram and paroxetine controlled-release treatment groups based on an analysis of covariance model using the baseline value as a covariate. Incidences of individual adverse events during the study were compared between the treatment groups using a chi-square test. The final dose of antidepressants was evaluated based on the fluoxetine equivalent. The statistical power regarding the primary outcome for efficacy was also calculated (alpha =0.5, http://www.biostat.ucsf.edu/sampsiz.html).

Statistical analyses were performed using Statistical Package for the Social Sciences Statistics for Windows (Version 22.0; Corporation, Armonk, NY, USA) and JMP (JMP 12.2. 1J; SAS Japan Inc., Tokyo, Japan). A P-value of <0.05 was considered statistically significant for all tests.

Results
The demographics and other characteristics of the patients are presented in Table 1. A total of 88 patients were recruited, all of whom were diagnosed with MDD at enrollment. Of these, 77.3% were first-episode patients and 61.4% were male, and the mean age was 40.8 ± 13.4 years. There were no significant differences in most variables between the treatment groups (Table 1).

Table 1 Baseline characteristics of the patients

| Variable                                 | Escitalopram (n=43) | Paroxetine controlled release (n=45) | Group difference | P-value |
|------------------------------------------|---------------------|--------------------------------------|------------------|---------|
| Male (%)                                 | 25 (58.1)           | 29 (64.4)                            | χ²=0.369         | 0.544   |
| Age, years (mean ± SD)                   | 38.9±12.4           | 42.5±14.2                            | t=-1.28         | 0.205   |
| First episode (%)                        | 35 (81.4)           | 33 (73.3)                            | χ²=0.819         | 0.366   |
| Educational history, years (mean ± SD)   | 14.0±1.88           | 13.6±2.22                            | t=-0.752        | 0.454   |
| Hospitalization (%)                      | 0 (0.00)            | 1 (2.22)                             | χ²=1.35         | 0.245   |
| Study center (FhU hospital, %)           | 19 (44.2)           | 26 (57.8)                            | χ²=1.63         | 0.202   |
| Married (%)                              | 25 (58.1)           | 19 (42.2)                            | χ²=2.24         | 0.135   |
| Unemployed (%)                           | 8 (18.6)            | 12 (26.7)                            | χ²=0.819        | 0.366   |
| Current smoker (%)                       | 9 (20.9)            | 9 (20.0)                             | χ²=0.012        | 0.914   |
| Hamilton Depression Rating Scale-17 total scores (mean ± SD) | 23.7±3.58          | 23.2±3.78                            | t=-0.605        | 0.547   |
| Hamilton Depression Rating Scale-21 total scores (mean ± SD) | 25.8±4.24          | 25.1±4.71                            | t=-0.710        | 0.480   |
| Comorbid psychiatric illness (%)a       | 6 (14.0)            | 6 (13.3)                             | χ²=0.007        | 0.933   |
| Body weight, kg (mean ± SD)              | 65.0±13.9           | 65.7±12.3                            | t=0.240         | 0.811   |
| Use of antidepressant (%)                | 0 (0.00)            | 0 (0.00)                             | Not applicable  |         |
| Use of hypnotic (%)                      | 6 (14.0)            | 6 (13.3)                             | χ²=0.007        | 0.933   |
| Use of anxiolytic (%)                    | 0 (0.00)            | 1 (2.22)                             | χ²=1.35         | 0.245   |

Note: aGeneralized anxiety disorder and/or panic disorder.
Abbreviations: FhU, Fujita Health University; SD, standard deviation.
The discontinuation rate was 58.0% (escitalopram, 55.8% and paroxetine controlled release, 60.0%; Table 2). There was no significant difference in the mean times to discontinuation between the escitalopram and paroxetine controlled-release treatment groups (13.4±10.1 vs 13.2±9.92 weeks; \( \chi^2(1) = 0.0836, P = 0.773 \)). All 88 patients were included in the efficacy and safety analyses. The mean escitalopram and paroxetine controlled-release doses at endpoint were 13.6±5.81 mg/day (fluoxetine equivalent, 30.2±12.9 mg/day) and 24.8±13.3 mg/day (fluoxetine equivalent, 29.2±15.7 mg/day), respectively (\( t(87) = 0.0836, P = 0.773 \)).

Both escitalopram and paroxetine controlled-release treatments were associated with significant improvements in the HAMD-21 and HAMD-17 total scores at 2, 4, 8, 12, and 24 weeks (Table S1). However, there were no significant differences in the magnitude of the HAMD-21, and HAMD-17 total score decreases at any time between the escitalopram and paroxetine controlled-release treatment groups (Table 3). The statistical power with respect to the primary outcome was 43%. Also, there were no significant differences in the response rate at any time point between the treatment groups (Figures 1 and 2).

No patients had serious adverse events such as death, suicide attempt, and serotonin syndrome, and there were no significant differences in the incidence of individual adverse events between the groups (Table 4). Moreover, there were no significant differences in body weight at the endpoint between the treatment groups (Table 4).

**Discussion**

This is the first randomized trial involving a comparison between escitalopram and paroxetine controlled release in Japanese patients with MDD. There were no significant differences in the efficacy and safety outcomes between the escitalopram and paroxetine controlled-release treatment groups in this study. However, our study found that discontinuation rates due to adverse events in both treatment

### Table 2 Discontinuation rate

| Number of patients | Escitalopram | Paroxetine controlled release |
|--------------------|--------------|-------------------------------|
| Randomized         | 43           | 45                            |
| Completed the trial (%) | 19 (44.2)    | 18 (40.0)                     |
| Discontinued the trial (%) | 24 (55.8)    | 27 (60.0)                     |

### Table 3 Group difference in Hamilton Depression Rating Scale scores at 2, 4, 8, 12, and 24 weeks

| Hamilton Depression Rating Scale-17 total scores | Escitalopram | Paroxetine controlled release |
|--------------------------------------------------|--------------|-------------------------------|
| Baseline                                         | 23.7±3.58    | 23.3±3.78                     |
| Change in score at 2 weeks                       | -9.4±0.67    | -7.1±0.76                     |
| F<sub>p</sub>-value                               | 0.161        | 0.169                         |
| Change in score at 4 weeks                       | -10.0±0.71   | -8.0±0.81                     |
| F<sub>p</sub>-value                               | 0.084        | 0.082                         |
| Change in score at 8 weeks                       | -12.0±0.71   | -10.1±0.83                    |
| F<sub>p</sub>-value                               | 0.314        | 0.312                         |
| Change in score at 12 weeks                      | -13.5±0.71   | -11.4±0.84                    |
| F<sub>p</sub>-value                               | 0.089        | 0.087                         |
| Change in score at 24 weeks                      | -15.5±0.71   | -13.5±0.84                    |
| F<sub>p</sub>-value                               | 0.084        | 0.082                         |
| Change in score at 24 weeks                      | -12.5±0.71   | -10.6±0.83                    |
| F<sub>p</sub>-value                               | 0.089        | 0.087                         |

### Table 4 Reasons of discontinuation

| Reason                | Escitalopram | Paroxetine controlled release |
|-----------------------|--------------|-------------------------------|
| Inefficacy (%)        | 9 (20.9)     | 8 (17.8)                      |
| Adverse events (%)    | 8 (18.6)     | 11 (24.4)                     |
| Other reasons (%)     | 7 (16.2)     | 8 (17.8)                      |
groups were relatively high compared with other studies on SSRIs. In a recent network meta-analysis, escitalopram emerged as the most efficacious agent among the SSRIs and was the best tolerated of the new-generation antidepressants (eg, agomelatine, duloxetine, escitalopram, fluvoxamine, fluoxetine, mirtazapine, paroxetine, sertraline, trazodone, and venlafaxine) that were analyzed. We did not find significant differences in any efficacy outcome between the escitalopram and paroxetine controlled-release treatment groups in this study. The statistical power with respect to the primary outcome was 43%. Therefore, our results might be a statistical error due to an insufficient sample size.
Table 4 Adverse events observed in the study (incidence ≥ 5%)

| Individual adverse events | Escitalopram (n=43) | Paroxetine controlled release (n=45) | Group difference ($\chi^2$ test or analysis of covariance and P-value) |
|---------------------------|---------------------|-------------------------------------|---------------------------------------------------------------|
| At least one adverse event (%) | 26 (60.5)           | 29 (64.4)                           | $\chi^2=0.149$ and 0.700                                      |
| Headache (%)               | 5 (11.6)            | 2 (4.44)                            | $\chi^2=1.59$ and 0.207                                      |
| Somnolence (%)             | 12 (27.9)           | 8 (17.8)                            | $\chi^2=1.29$ and 0.256                                      |
| Dizziness (%)              | 6 (14.0)            | 4 (8.89)                            | $\chi^2=0.562$ and 0.453                                    |
| Anxiety (%)                | 9 (20.9)            | 4 (8.89)                            | $\chi^2=2.58$ and 0.108                                     |
| Insomnia (%)               | 6 (14.0)            | 5 (11.1)                            | $\chi^2=0.162$ and 0.687                                    |
| Decreased salivation (%)   | 3 (6.98)            | 5 (11.1)                            | $\chi^2=0.460$ and 0.498                                    |
| Nausea/vomiting (%)        | 11 (25.6)           | 12 (26.7)                           | $\chi^2=0.013$ and 0.908                                    |
| Diarrhea (%)               | 9 (20.9)            | 6 (13.3)                            | $\chi^2=0.901$ and 0.342                                    |
| Constipation (%)           | 6 (14.0)            | 3 (6.67)                            | $\chi^2=1.29$ and 0.256                                    |
| Use of sexual desire (%)   | 2 (4.65)            | 3 (6.67)                            | $\chi^2=0.168$ and 0.682                                    |
| Use of hypnotic (%)        | 6 (14.0)            | 6 (13.3)                            | $\chi^2=0.007$ and 0.933                                    |
| Use of anxiolytic (%)      | 0 (0.00)            | 1 (2.22)                            | $\chi^2=1.35$ and 0.245                                    |
| Weight gain (%)            | 1 (2.33)            | 3 (6.67)                            | $\chi^2=1.00$ and 0.317                                    |
| Mean weight change (kg)*   | 0.85±3.05           | 0.50±2.11                           | $F_{1,89}=0.471$ and 0.494                                  |

Notes: *Covariate: body weight at baseline. Data presented as mean ± standard deviation.

Limitations

One of the primary limitations of this study is that the study was not double blinded. The physicians responsible for assessing the adverse events were aware of which treatment was received by which patient. Although the raters were masked to the nature of the antidepressant treatment and were not involved in any side effect ratings or management decisions, it is possible that they were inadvertently informed of the group allocation by the patients. The second limitation is that this study did not include a placebo arm. The third limitation is the small sample size, particularly in the subgroup analysis (the statistical power with respect to the primary outcome was 43%). Therefore, we did not perform an HAMD item analysis. The fourth limitation is that we did not correct for multiple comparisons (eg, using Bonferroni's correction), because the application of a more stringent alpha level for secondary outcomes would have been too conservative in this small sample.14,15 The fifth one is that we did not count the number of patients who were screened for entry in the study. Finally, the intent-to-treat analysis using the last observation carried forward method may have influenced the results. The discontinuation rate was high, and thus, this method may yield a biased estimate of the treatment effect and underestimate the variability of the results.16 It is not clearly justified why this analysis, in particular, is appropriate and valid. However, if we had selected a complete analysis, our sample size would have been too small.

Conclusion

In conclusion, our findings suggest that although escitalopram and paroxetine controlled release are effective in patients with MDD, discontinuation rates due to adverse events in both treatment groups were relatively high. However, because our study might be underpowered to detect significant differences in efficacy and safety outcomes between the escitalopram and paroxetine controlled-release treatment groups, further study using a larger sample size is required.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

### Table S1 Endpoint change in Hamilton Depression Rating Scale scores at 2, 4, 8, 12, and 24 weeks from the baseline

| Endpoint change at baseline | Mean score at 2 weeks | t<sub>df</sub>, P-value | Mean score at 4 weeks | t<sub>df</sub>, P-value | Mean score at 8 weeks | t<sub>df</sub>, P-value | Mean score at 12 weeks | t<sub>df</sub>, P-value | Mean score at 24 weeks | t<sub>df</sub>, P-value |
|-----------------------------|-----------------------|------------------------|-----------------------|------------------------|-----------------------|------------------------|-----------------------|------------------------|-----------------------|------------------------|
| Hamilton Depression Rating Scale-17 total score: escitalopram | 23.7±3.58 | t<sub>df</sub>=−9.38, <0.0001 | 11.7±6.37 | t<sub>df</sub>=−11.2, <0.0001 | 10.9±6.71 | t<sub>df</sub>=−11.4, <0.0001 | 10.3±7.00 | t<sub>df</sub>=−11.6, <0.0001 | 9.23±7.24 | t<sub>df</sub>=−12.3, <0.0001 |
| Hamilton Depression Rating Scale-17 total score: paroxetine controlled release | 23.2±3.78 | t<sub>df</sub>=−6.57, <0.0001 | 13.6±7.63 | t<sub>df</sub>=−8.28, <0.0001 | 12.3±7.64 | t<sub>df</sub>=−9.61, <0.0001 | 12.6±7.67 | t<sub>df</sub>=−9.03, <0.0001 | 11.4±7.86 | t<sub>df</sub>=−9.72, <0.0001 |
| Hamilton Depression Rating Scale-21 total score: escitalopram | 25.8±4.24 | t<sub>df</sub>=−9.15, <0.0001 | 13.2±7.41 | t<sub>df</sub>=−10.3, <0.0001 | 12.0±7.58 | t<sub>df</sub>=−11.3, <0.0001 | 10.4±7.76 | t<sub>df</sub>=−13.0, <0.0001 | 10.1±7.97 | t<sub>df</sub>=−12.6, <0.0001 |
| Hamilton Depression Rating Scale-21 total score: paroxetine controlled release | 25.1±4.71 | t<sub>df</sub>=−6.50, <0.0001 | 14.8±8.82 | t<sub>df</sub>=−8.00, <0.0001 | 13.1±8.79 | t<sub>df</sub>=−9.55, <0.0001 | 13.1±9.27 | t<sub>df</sub>=−8.95, <0.0001 | 11.6±9.62 | t<sub>df</sub>=−9.61, <0.0001 |

**Note:** Data presented as mean ± standard deviation.

**Abbreviation:** df, degrees of freedom.
