Changes in Antithrombotic Therapy Over Time and Durability of a Prasugrel WOEST-Like Regimen for Percutaneous Coronary Intervention Patients With Atrial Fibrillation — Post Hoc Analysis of the PENDULUM Mono and PENDULUM Registries —

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Background: Previously published randomized atrial fibrillation (AF) percutaneous coronary intervention (PCI) trials have demonstrated the safety and efficacy of a WOEST-like regimen (oral anticoagulant [OAC] plus P2Y12 inhibitor) in patients with AF PCI within 1 year. However, the efficacy of this regimen in real-world practice has not been fully confirmed, especially the efficacy of the WOEST-like regimen using the approved dose of prasugrel in Japan.

Methods and Results: This post hoc analysis included 186 and 220 patients from the PENDULUM mono and PENDULUM registries, respectively. Endpoints were the cumulative incidences of clinically relevant bleeding (CRB) and major adverse cardiac and cerebrovascular events (MACCE) at 12 months after PCI. Differences in the enrollment period led to an increase in OAC prescriptions (from 64.7% to 81.2%) and a reduction in the median duration of triple antithrombotic therapy (from 203.0 to 32.0 days) in the PENDULUM vs. PENDULUM mono registries, respectively. After adjustment by the inverse probability of treatment method, in patients with OAC, PENDULUM mono AF significantly reduced CRB without increasing MACCE compared with PENDULUM AF.

Conclusions: A WOEST-like regimen with prasugrel may reduce CRB, without increasing MACCE, in Japanese patients with AF and high bleeding risk undergoing PCI.

Key Words: Atrial fibrillation; Bleeding; Japan; Percutaneous coronary intervention; Prasugrel
Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention: Studies compared the safety and efficacy of dual antithrombotic therapy (WOEST-like regimen: concomitant use of an oral anticoagulant [OAC] and a P2Y<sub>12</sub> inhibitor) and triple antithrombotic therapy (TAT; concomitant use of an OAC, P2Y<sub>12</sub> inhibitor, and aspirin) in patients undergoing percutaneous coronary intervention (PCI) complicated by atrial fibrillation (AF). These studies have established the efficacy and safety of the WOEST-like regimen and have led to its adoption in recent guidelines. However, this evidence was obtained outside of Japan and, more importantly, does not include patients treated with the Japanese-specific dose of prasugrel (3.75 mg). Patients were enrolled in the PENDULUM and PENDULUM mono registries from 2015 to 2018, at a time when a large amount of evidence on antithrombotic therapy for AF PCI patients had been accumulated through randomized controlled trials (RCTs). Although the Japanese Society of Cardiology guidelines had not been revised at that time, such evidence may not only reflect physicians’ prescriptions, but may also influence prescribing patterns. Therefore, analysis of AF PCI patients in the PENDULUM and PENDULUM mono registries may provide deep insights into the antithrombotic management of AF PCI in real-world practice. To clarify the impact of these prescription changes on outcomes, we analyzed the relationship between these changes and clinical outcomes. In particular, this study focused on the WOEST-like regimen with prasugrel.

Methods

Study Design

This was a post hoc analysis of 2 multicenter non-interventional prospective registration studies (PENDULUM mono and PENDULUM mono). Specifically, we conducted a post hoc subgroup analysis of patients from a previously published historical comparison of the PENDULUM mono and PENDULUM registries who presented with AF.

The study protocols for the PENDULUM and PENDULUM mono studies were approved by the Ethics Committee of Toho University Ohashi Medical Center on 14 December 2015 (Reference code: 15-71) and 31 May 2017 (Reference code: H17006), respectively. Both studies were performed in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent. PENDULUM mono also complied with the Guidelines on Standards for the Conduct of Clinical Trials of Medicinal Products of the International Conference on Harmonization of Medicinal Products Regulations of the United States, Japan, and the European Union. Both studies were registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry under the identifier numbers UMIN000028023 (PENDULUM mono) and UMIN000020332 (PENDULUM).

Study Population

Patients eligible for this analysis were AF patients from PENDULUM mono enrolled between June 2017 and December 2018 (197 of 1,222) and those from PENDULUM enrolled between December 2015 and July 2017 (538 of 6,422). The full inclusion and exclusion criteria for patients in the PENDULUM mono and PENDULUM registries have been described previously. This was an intention-to-treat analysis, and patients were analyzed if they were prescribed prasugrel as the P2Y<sub>12</sub> inhibitor on the day of PCI (n=197 and 249 in PENDULUM mono and PENDULUM, respectively).

Outcomes

The endpoints were the cumulative incidences of clinically relevant bleeding (CRB; Bleeding Academic Research Consortium [BARC] Types 2, 3, and 5), major bleeding (BARC Types 3 and 5), and major adverse cardiac and cerebrovascular events (MACCE) 12 months after PCI. MACCE was defined as all-cause death, non-fatal myocardial infarction, non-fatal stroke, and stent thrombosis occurring 12 months after the index PCI. Bleeding risk at the time of PCI was evaluated using the mean number of high bleeding risk (HBR) criteria.

Statistical Analysis

A propensity score method was used to reduce the effect of treatment selection bias and potential confounders, and thus objectively compare data from the PENDULUM mono and PENDULUM regimens. Age, body weight, estimated glomerular filtration rate, hemoglobin, direct OAC (DOAC) use at discharge, diabetes mellitus, acute coronary syndrome, platelet count, peripheral artery disease, gastrointestinal bleeding, non-steroidal anti-inflammatory drug/steroid use at discharge, ischemic stroke/transient ischemic attack/intracerebral hemorrhage, and complex PCI were the variables used in multivariate logistic regression to calculate the propensity scores. These variables were chosen based on the Japanese Circulation Society 2020 guideline and a previous report. Background bias of patients enrolled in both studies was adjusted using the inverse probability treatment weighting (IPTW) method. Standardized mean differences were calculated for baseline characteristics to verify the confounders’ balance between the 2 groups.

The dual antiplatelet therapy (DAPT) discontinuation rate was calculated based on patients who discontinued either aspirin or P2Y<sub>12</sub>. If these patients restarted DAPT later, they were excluded from the analysis of DAPT discontinuation. The DAPT and TAT discontinuation rates were estimated using the Kaplan-Meier method.

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The Kaplan-Meier method was used to calculate the cumulative incidences of CRB, major bleeding, and MACCE and the corresponding 95% confidence intervals (CIs) at 12 months before and after adjusting for background factors using the IPTW method. The Cox regression model was used to calculate hazard ratios (HRs) and 95% CIs. The risk of MACCE and BARC 2, 3, or 5 bleeding events according to antithrombotic treatment regimen was estimated using Cox regression models. Statistical significance was set at two-sided P<0.05. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patient Characteristics

Patient disposition is shown in Figure 1. Of the 1,222 patients in PENDULUM mono, 197 patients with AF were included in this study. Of these, 186 patients with propensity scores were evaluated (PENDULUM mono AF). Among the 6,422 patients enrolled in PENDULUM, 249 patients with AF were included in this study. Of these, 220 patients with propensity scores were evaluated (PENDULUM AF).

The characteristics of AF patients before propensity score weighting are presented in Table 1. Patient background characteristics after adjustment and standardized mean differences after adjustment are presented in Supplementary Table 1. The most common comorbidity was hypertension. In the PENDULUM mono AF and PENDULUM AF groups, 18.8% and 14.9% of patients, respectively, had a history of ischemic stroke and 4.6% and 2.8%, respectively, had a history of intracranial hemorrhage. Clinical manifestations included acute coronary syndrome in 26.4% and 31.7% of patients in the PENDULUM mono AF and PENDULUM AF groups, respectively. Mean±SD CHADS₂ scores before adjusting for background factors using the IPTW method were 2.7±1.2 and 2.4±1.2 in the PENDULUM mono AF and PENDULUM AF groups, respectively (Supplementary Table 2).

Changes in Antithrombotic Prescription

The percentage of patients without OACs at discharge decreased from 35.3% in the PENDULUM AF group to 18.8% in the PENDULUM mono AF group. This was accompanied by an increase in the prescription of DOACs in the PENDULUM AF group vs. the PENDULUM mono AF group (from 47.8% to 67.5%). In the case of antiplatelet administration, the mean duration of DAPT was 61.7 days in the PENDULUM mono AF group and 199.0 days in the PENDULUM AF group, whereas the median duration of DAPT therapy was 32 days in the PENDULUM mono AF group and 203 days in the PENDULUM AF group (Supplementary Figure).

Outcomes

The cumulative incidence of CRB (BARC Types 2, 3, and 5) at 12 months after PCI was 8.1% in the PENDULUM mono AF group and 9.2% in the PENDULUM AF group (HR 0.81; 95% CI 0.41–1.58; P=0.528; Figure 2A). The cumulative incidence of major bleeding (BARC Types 3 and 5) at 12 months after PCI was 6.4% in the PENDULUM mono AF group and 7.5% in the PENDULUM AF group (HR 0.77; 95% CI 0.37–1.64; P=0.502; Figure 2B). The
cumulative incidence of MACCE at 12 months after PCI did not tend to increase in the PENDULUM mono AF group and did not differ from that in the PENDULUM AF group (HR 0.88; 95% CI 0.41–1.90; P=0.752; Figure 2C).

Comparison Between PENDULUM Mono AF and PENDULUM AF Patients With and Without OAC Use
The incidences of CRB and MACCE in the PENDULUM mono AF and PENDULUM AF groups with and without anticoagulant use before IPTW adjustment are presented in Table 2. In both the PENDULUM mono AF and PENDULUM AF groups, the incidence of MACCE was two to threefold higher in patients who were treated with antiplatelet agents only. The incidence of CRB was high in the PENDULUM AF group with OAC, but higher in the PENDULUM mono AF group without OAC.

Differences in the Timing of Initiation of the WOEST-Like Regimen
The cumulative incidences of CRB, major bleeding, and MACCE after IPTW adjustment are shown in Figure 3. Bleeding events were numerically higher in the PENDULUM AF group, including both patients with and without OACs. The cumulative incidences of CRB, major bleeding,

### Table 1. Characteristics of Patients With AF Before Adjusting for Background Factors Using the Inverse Probability Treatment Weighting Method

| Characteristic                        | PENDULUM mono AF (n=197) | PENDULUM AF (n=249) | Standardized mean difference |
|--------------------------------------|--------------------------|---------------------|-----------------------------|
| Age (years)                          | 75.9±8.0                 | 74.0±8.4            | 0.236                       |
| Male sex                             | 148 (75.1)               | 192 (77.1)          | −0.046                      |
| Body weight (kg)                     | 60.6±11.6                | 62.7±13.0           | −0.172                      |
| Hypertension                         | 173 (87.8)               | 211 (84.7)          | 0.090                       |
| Hyperlipidemia                       | 140 (71.1)               | 174 (69.9)          | 0.026                       |
| Diabetes mellitus                    | 74 (37.6)                | 99 (39.8)           | −0.045                      |
| Current smoker                       | 19 (9.6)                 | 49 (19.7)           | −0.287                      |
| Heart failure                        | 60 (30.5)                | 75 (30.1)           | 0.007                       |
| Peripheral arterial disease          | 16 (8.1)                 | 14 (5.6)            | 0.099                       |
| Atrial fibrillation                  | 197 (100.0)              | 249 (100.0)         | –                          |
| Malignancy                           | 16 (8.1)                 | 26 (10.4)           | −0.080                      |
| History                              |                          |                     |                             |
| Myocardial infarction                | 42 (21.3)                | 64 (25.7)           | −0.103                      |
| PCI                                  | 74 (37.6)                | 96 (38.6)           | −0.020                      |
| CABG                                 | 8 (4.1)                  | 10 (4.0)            | 0.002                       |
| Ischemic stroke                      | 37 (18.8)                | 37 (14.9)           | 0.105                       |
| ICH                                  | 9 (4.6)                  | 7 (2.8)             | 0.093                       |
| Gastrointestinal bleeding            | 15 (7.6)                 | 15 (6.0)            | 0.063                       |
| Clinical presentation                |                          |                     |                             |
| Non-ACS                              | 145 (73.6)               | 170 (68.3)          | 0.118                       |
| ACS                                  | 52 (26.4)                | 79 (31.7)           | −0.118                      |
| Unstable angina                      | 27 (13.7)                | 29 (11.6)           | 0.062                       |
| NSTEMI                               | 14 (7.1)                 | 15 (6.0)            | 0.044                       |
| STEMI                                | 11 (5.6)                 | 35 (14.1)           | −0.288                      |
| Baseline laboratory values           |                          |                     |                             |
| Hemoglobin (g/dL)                    | 12.9±1.8                 | 12.9±2.0            | 0.013                       |
| eGFR (mL/min/1.73m²)                 | 50.8±20.9                | 54.4±22.4           | −0.169                      |
| WBC (x10^9/L)                        | 6.2±1.9                  | 6.9±2.4             | −0.319                      |
| Platelet count (x10^4/μL)            | 19.6±6.9                 | 20.9±6.5            | −0.201                      |
| Medication at discharge              |                          |                     |                             |
| Prasugrel                            | 196 (99.5)               | 226 (90.8)          | 0.414                       |
| 3.75 mg                              | 184 (93.4)               | 225 (90.4)          | 0.111                       |
| 2.5 mg                               | 12 (6.1)                 | 1 (0.4)             | 0.325                       |
| Clopidogrel                          | 0 (0.0)                  | 21 (8.4)            | −0.429                      |
| Aspirin                              | 155 (78.7)               | 242 (97.2)          | −0.593                      |
| Anticoagulant                        | 160 (81.2)               | 161 (64.7)          | 0.379                       |
| DOAC                                 | 133 (67.5)               | 119 (47.8)          | 0.407                       |
| Warfarin                             | 27 (13.7)                | 42 (16.9)           | −0.088                      |
| PPI                                  | 174 (88.3)               | 219 (88.0)          | 0.012                       |
| NSAIDs (except aspirin)              | 12 (6.1)                 | 17 (6.8)            | −0.030                      |
| Steroids                             | 8 (4.1)                  | 14 (5.6)            | −0.073                      |

(Table 1 continued the next page.)
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Discussion

The present multicenter study is the first to evaluate the use of the prasugrel maintenance dose marketed in Japan (3.75 mg) for Japanese patients with AF and HBR who underwent PCI. The frequency of AF PCI was 8.3%, consistent with the reported frequency in large PCI registries (CREDO-Kyoto).14 In contrast, AF PCI was 16.1% in

and MAACE in patients treated with OACs from the PENDULUM mono AF and PENDULUM AF groups after IPTW adjustment are shown in Figure 4. In the PENDULUM mono AF group, the cumulative incidence of CRB was significantly lower than in the PENDULUM AF group without any increase in MACCE.

**Cox Regression Analysis of Different Antithrombotic Regimens**

Figure 5 shows the difference in outcomes by different antithrombotic regimens for AF patients who underwent PCI with the WOEST-like regimen as a reference. Although there was a difference between the WOEST-like and TAT regimes in terms of CRB, there were no statistically significant differences between the WOEST-like regimen and other formulations, although there was a tendency for the WOEST-like formulation to show benefits.

| Characteristic | PENDULUM mono AF (n=197) | PENDULUM AF (n=249) | Standardized mean difference |
|---------------|--------------------------|---------------------|-----------------------------|
| Angiographic features |                           |                     |                             |
| No. diseased vessels |                           |                     |                             |
| 1             | 101 (51.3)               | 104 (41.8)          | 0.191                       |
| 2             | 60 (30.5)                | 83 (33.3)           | −0.062                      |
| 3             | 34 (17.3)                | 57 (22.9)           | −0.141                      |
| Left main trunk | 8 (4.1)                  | 17 (6.8)            | −0.122                      |
| Procedural data |                           |                     |                             |
| Puncture site  |                           |                     |                             |
| Femoral       | 38 (19.3)                | 76 (30.5)           | −0.262                      |
| Brachial       | 11 (5.6)                 | 12 (4.8)            | 0.034                       |
| Radial         | 147 (74.6)               | 164 (65.9)          | 0.192                       |
| Imaging-guided |                           |                     |                             |
| IVUS or OCT/OFDI | 186 (94.4)             | 234 (94.0)          | 0.019                       |
| Complex PCI    |                           |                     |                             |
| All            | 35 (17.8)                | 55 (22.1)           | −0.108                      |
| ≥3 stents      | 13 (6.6)                 | 19 (7.6)            | −0.040                      |
| ≥3 treatment lesions | 13 (6.6)            | 20 (8.0)           | −0.055                      |
| Bifurcation with 2 stents | 2 (1.0)          | 3 (1.2)            | −0.018                      |
| Total stent length >60 mm | 23 (11.7)      | 27 (10.8)          | 0.026                       |
| Chronic total occlusion | 11 (5.6)      | 20 (8.0)          | −0.097                      |
| HBR criteria   |                           |                     |                             |
| HBR            | 193 (98.0)               | 224 (90.0)          | 0.341                       |
| OAC use        | 160 (81.2)               | 161 (64.7)          | 0.379                       |
| Severe CKD (eGFR <30mL/min/1.73m²) | 26 (13.2) | 28 (11.2) | 0.060 |
| Severe anemia (Hb <11 g/dL) | 32 (16.2) | 48 (19.3) | −0.079 |
| Platelet count <100x10⁹/L | 5 (2.5) | 7 (2.8) | −0.017 |
| Liver cirrhosis | 0 (0.0)                  | 1 (0.4)             | −0.090                      |
| Malignancy     | 16 (8.1)                 | 26 (10.4)           | −0.080                      |
| Prior ICH      | 9 (4.6)                  | 7 (2.8)             | 0.093                       |
| Age ≥75 years  | 126 (64.0)               | 119 (47.8)          | 0.330                       |
| Moderate CKD (eGFR 30–<60mL/min/1.73m²) | 101 (51.3) | 112 (45.0) | 0.126 |
| Moderate anemia (Hb 11–13 g/dL in men, 11–12 g/dL in women) | 49 (24.9) | 57 (22.9) | 0.046 |
| NSAIDs or steroid use | 17 (8.6)     | 26 (10.4)          | −0.062                      |
| Prior ischemic stroke without ICH | 33 (16.8) | 34 (13.7) | 0.086 |
| Prior gastrointestinal bleeding | 15 (7.6)     | 15 (6.0)          | 0.063                       |

Unless indicated otherwise data are given as n (%) or as the mean ± SD. ACS, acute coronary syndrome; AF, atrial fibrillation; CABG, coronary artery bypass graft; CKD, chronic kidney disease; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HBR, high bleeding risk; ICH, intracranial hemorrhage; IVUS, intravascular ultrasound; NSAIDs, non-steroidal anti-inflammatory drugs; NSTEMI, non-ST segment elevation myocardial infarction; OAC, oral anticoagulant; OCT, optical coherence tomography; OFDI, optical frequency domain imaging; PCI, percutaneous coronary intervention; PPI, proton-pump inhibitor; STEMI, ST-elevation myocardial infarction; WBC, white blood cell count.
Safety and Efficacy of Prasugrel in AF PCI

Figure 2. Cumulative incidence before inverse probability treatment weighting adjustment of (A) clinically relevant bleeding (Bleeding Academic Research Consortium [BARC] Types 2, 3, and 5), (B) major bleeding (BARC Types 3 and 5), and (C) major adverse cardiac and cerebrovascular events (MACCE). AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio.
Table 2. Comparison of the Incidence of CRB and MACCE in the PENDULUM Mono AF and PENDULUM AF Groups According to OAC Use Before Inverse Probability Treatment Weighting Adjustment

|                      | With OAC | Without OAC |
|----------------------|----------|-------------|
|                      | PENDULUM mono AF (n=160) | PENDULUM AF (n=161) | PENDULUM mono AF (n=37) | PENDULUM AF (n=88) |
| CRB                  | 10 (6.9) | 18 (11.2)   | 4 (10.8)       | 4 (4.5)       |
|                       | 0.55 (0.25–1.19) | 1.19 (0.40–3.54) | 2.49 (0.62–10.00) | 0.98 (0.31–3.13) |
| MACCE                | 7 (4.4)  | 6 (3.7)     | 4 (10.8)       | 10 (11.4)     |
|                       | 1.19 (0.40–3.54) | 0.98 (0.31–3.13) |                  |               |

Unless indicated otherwise data show the number of patients in each group with the percentage in parentheses. AF, atrial fibrillation; CI, confidence interval; CRB, clinically relevant bleeding; HR, hazard ratio; MACCE, major adverse cardiac and cerebrovascular events; OAC, oral anticoagulant.

Figure 3. Cumulative incidence after inverse probability treatment weighting adjustment of (A) clinically relevant bleeding (Bleeding Academic Research Consortium [BARC] Types 2, 3, and 5), (B) major bleeding (BARC Types 3 and 5), and (C) major adverse cardiac and cerebrovascular events (MACCE). AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio.
Safety and Efficacy of Prasugrel in AF PCI

PENDULUM mono, which registered patients with HBR. This suggests that AF PCI is a major contributor to HBR in routine practice and is clinically significant. The uniqueness of this study is that patient enrollment occurred at a time when much of the evidence for AF PCI was accumulating. In addition, the prescription of antithrombotic therapy was left to the discretion of physicians. Therefore, antithrombotic therapy is presumed to vary over time, and studies on trends in prescribing may provide different antithrombotic outcomes for AF PCI. In particular, because...
AF compared with PENDULUM AF. This finding is consistent with previous AF PCI RCTs and important because this is the first study to show that a WOEST-like regimen can reduce the risk of bleeding without increasing the risk of MACCE in Japanese patients at the dose of 3.75 mg, which is approved in Japan.

Regarding the balance of bleeding and thrombosis risk, Cox regression analysis in the present study may suggest that a WOEST-like regimen with prasugrel is optimal. The reason for the lack of statistical significance is most likely insufficient power, but this finding is consistent with a previous large cohort study from Denmark\textsuperscript{16} and subsequent AF PCI RCTs.\textsuperscript{17,18} The results observed in this study are practical and meaningful for daily practice because the study used real-world data from the latest PCI procedures without any notable exclusions.

Study Limitations

The present study was not an RCT, but a matched trial of existing controls. For consistency with PENDULUM mono, the factors used to calculate propensity scores in the present study are unified with PENDULUM mono. OAC use at discharge was adjusted using the IPTW method and the comparison between the 2 groups was balanced; however, the rate of OAC prescription in this study differed between the groups. Therefore, there may be unadjusted confounders, such as ST-elevation myocardial infarction. Because of the observational study design, we could not thoroughly examine the benefits of the WOEST-like regimen with prasugrel. Furthermore, because of the study’s observational nature, it was difficult to determine the optimal duration of TAT. Regarding adverse events, the possibility of evaluator bias cannot be excluded. Although the evaluators were the same, the pre-existing controlled trial design allowed the adverse event evaluators to know whether participants were in the PENDULUM mono AF or PENDULUM AF group. Event occurrences in this study were determined by physician judgment (diagnosis), so clinical events may have been underreported. Because this was a post hoc analysis,
it lacks statistical power. In addition, the sample size was not designed with the objective of detecting statistical differences between AF subgroups. This study did not focus on AF, and thus detailed data on the type of AF cannot be provided. Therefore, it would be necessary to conduct an analysis with more AF patients in a future RCT.

Conclusions

The findings of the present study suggest that a WOEST-like regimen with prasugrel may reduce BARC Types 2, 3, and 5 bleeding, without increasing MACCE, in Japanese patients with AF undergoing PCI.

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IRB Information

This is a post hoc analysis of data from the PENDULUM mono and PENDULUM registry studies conducted in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent. Protocols for the PENDULUM registry and PENDULUM mono studies were approved by the Ethics Committee of Toho University Ohashi Medical Center on 14 December 2015 (Reference code: 15–71) and 31 May 2017 (Reference code: H17006), respectively. PENDULUM mono also complied with the Guidelines on Standards for the Conduct of Clinical Trials of Medicinal Products of the International Conference on Harmonization of Medicinal Products Regulations of the United States, Japan, and the European Union.

Data Availability

The deidentified participant data and study protocol will be shared on a request basis for up to 36 months after the publication of this article. Researchers who make the request should include a methodologically sound proposal on how the data will be used; the proposal may be reviewed by the responsible personnel at Daiichi Sankyo, and the data requestors will need to sign a data access agreement. Please contact the corresponding author directly to request data sharing.

Author Contributions

All authors provided substantial contributions to the conception or design of the study, or the acquisition, analysis, or interpretation of data; participated in drafting the manuscript or revising it critically for important intellectual content; provided final approval of the version to be published; and are in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the study are appropriately investigated and resolved.

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**Supplementary Files**

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