Effect of ipragliflozin on liver function in Japanese type 2 diabetes mellitus patients: a subgroup analysis of the STELLA-LONG TERM study (3-month interim results)

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Abstract. This subgroup analysis of STELLA-LONG TERM, an ongoing 3-year post-marketing surveillance study on the long-term efficacy and safety of ipragliflozin, assessed the effect of ipragliflozin on liver function in type 2 diabetes mellitus (T2DM) patients. Patients were divided according to baseline liver function (normal [male: ALT ≤30, female: ALT ≤20], abnormal [male: ALT ≥31, female: ALT ≥21]). We evaluated changes in aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (γ-GTP), alkaline phosphatase (ALP), and fatty liver index (FLI) at 3 months of treatment; the proportion of patients with abnormal liver function whose liver function normalized after 3 months of treatment; and correlations between changes in ALT levels and efficacy variables/laboratory values. Liver function was normal in 2,570 and abnormal in 3,239 patients. Only patients with abnormal liver function showed a statistically/clinically significant decrease in AST, ALT, γ-GTP, and ALP levels at 3 months (all \(p < 0.05\) vs. baseline). The FLI significantly decreased from 63.2677 ± 26.4363 (baseline) to 56.7137 ± 27.6484 (3 months) \(p < 0.05\) in the overall patient population. Liver function normalized in 20.5% (543/2,648) of patients with abnormal liver function. There was no obvious correlation between changes in ALT and changes in efficacy/laboratory parameters. Liver function improved after 3-month treatment with ipragliflozin in T2DM patients with abnormal liver function.

Key words: Ipragliflozin, Japan, Liver function, Post-marketing surveillance, Type 2 diabetes mellitus

ABNORMAL LIVER FUNCTION and non-alcoholic fatty liver disease (NAFLD) are frequent comorbidities in obese patients and type 2 diabetes mellitus (T2DM) patients. Diabetes patients are at risk of developing non-alcoholic steatohepatitis (NASH), a more aggressive form of NAFLD that involves liver damage [1]. Up to 70% of T2DM patients have NAFLD [2] and approximately 30%–40% of obese T2DM patients have NASH [1]. Among T2DM patients with proven NASH, approximately 20% have normal liver function tests [3]. Approximately 5%–7% of T2DM patients have clinically silent advanced hepatic fibrosis, which is one of the last stages of liver disease [4, 5]. NAFLD/NASH patients have a higher risk of hepatocellular carcinoma [6] and cardiovascular disease [7, 8]. Therefore, patients with impaired liver function may benefit from antidiabetic drugs that have the potential to improve liver function.

Ipragliflozin, a sodium–glucose cotransporter 2 (SGLT2) inhibitor, was approved for the treatment of T2DM patients in Japan in 2014 [9]. A pooled analysis of five randomized controlled trials showed that ipragliflozin improved liver function-related parameters (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and gamma-glutamyltransferase [γ-GTP]) in T2DM patients [10]. Several recent pre-clinical studies have discussed liver function improvement with the use of SGLT2 inhibitors [11–20]. However, there are insufficient data on the potential effects of ipragliflozin on liver function parameters of T2DM patients, particularly those with abnormal liver function.

The Specified drug use result of Ipragliflozin treatment in type 2 diabetic patients: LONG-TERM use (STELLA-LONG TERM) study is an ongoing 3-year prospective post-marketing surveillance study on the long-term efficacy and safety of ipragliflozin [21]. We performed a subgroup analysis of the STELLA-LONG TERM interim report [22] to provide further insight into the effect of ipragliflozin on liver function in T2DM patients, with a particular focus on patients with abnormal liver function. Here, we present the results of an interim analysis of the 3-month data stratified into two...
subgroups (patients with normal or abnormal baseline liver function).

**Materials and Methods**

This surveillance study complied with Good Post-marketing Study Practice and was performed as described previously [22]. This study was registered at ClinicalTrials.gov (NCT02479399).

The study design and methods have been described in the previous interim report [22]. Briefly, all Japanese T2DM patients who were first prescribed ipragliflozin between 17 July 2014 and 16 October 2015 at participating medical centers in Japan were registered in STELLA-LONG TERM. Patients with viral hepatitis comorbidity (hepatitis B virus and hepatitis C virus) were not excluded from the present subgroup analysis. Patients were divided into two subgroups as follows: those with normal liver function, defined as patients with baseline ALT ≤30 (male) or ≤20 (female) U/L, and those with abnormal liver function, defined as patients with baseline ALT ≥31 (male) or ≥21 (female) U/L.

In accordance with the package insert, patients received ipragliflozin 50 mg once daily before or after breakfast. A lower dose was permitted in patients with severe hepatic impairment at the attending physician’s discretion but was to be used with caution. A dose increase to 100 mg/day was allowed with careful monitoring of the patient’s clinical course if the treatment efficacy was judged to be insufficient by the treating physician.

Demographic and clinical characteristics, medication-related data, laboratory variables, vital signs (blood pressure and heart rate), and safety data (adverse events) were evaluated. Changes in liver function-related variables, including AST, ALT, γ-GTP, alkaline phosphatase (ALP), and fatty liver index, were compared between the two groups. The percentage of patients with abnormal liver function whose liver function normalized (i.e., ALT ≤30 [male] or ≤20 [female] U/L) and those with abnormal liver function, defined as patients with baseline ALT ≥31 (male) or ≥21 (female) U/L.

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The fatty liver index was calculated based on an algorithm proposed by Bedogni et al. [23]:

\[
\text{Fatty liver index} = \frac{0.093 \times \log (\text{triglycerides}) + 0.139 \times \text{BMI} + 0.718 \times \log (\text{gg}) + 0.053 \times \text{waist circumference} - 15.745}{1 + e^{-0.953 \times \log (\text{triglycerides}) + 0.139 \times \text{BMI} + 0.718 \times \log (\text{gg}) + 0.053 \times \text{waist circumference} - 15.745}} \times 100
\]

A fatty liver index <30 rules out hepatic steatosis, and a fatty liver index ≥60 indicates hepatic steatosis.

**Statistical analysis**

Sample size calculations and rationale for the study length were described previously [21]. No sample size calculation was considered regarding the subgroup comparisons. Efficacy variables, vital signs, and laboratory variables are presented as means ± standard deviations. Paired t-tests were used to assess changes from baseline. Categorical variables, including baseline characteristics, are shown as n (%) of patients. Patient characteristics were compared between the two groups using the two-sample t-test and chi-squared test. In the present subgroup analysis, we did not perform adjustments for type I error based on multiple hypothesis testing. Pearson’s correlation coefficient was calculated to evaluate the relationship between changes in ALT and changes in efficacy/laboratory parameters.

**Results**

**Patient disposition**

Fig. 1 shows the disposition of patients registered in this surveillance study. Of 2,431 institutions that agreed to participate in the study, 1,941 participated and initially registered 11,411 patients. Report forms were collected for 11,289 patients at 3 months. Out of 11,289 patients included in the locked database, the efficacy analysis set comprised 8,633 patients. The reasons for excluding patients from the efficacy analysis set are shown in Fig. 1.

**Patient characteristics**

Table 1 shows the general characteristics of patients in the efficacy analysis set. Of 8,633 patients in the efficacy analysis set, 2,570 (29.8%) and 3,239 (37.5%) patients had normal or abnormal liver function, respectively. Liver function data were missing from 2,824 (32.7%) patients. Compared with patients with normal liver function, a greater proportion of patients in the abnormal liver function subgroup were female, <65 years old, with shorter disease duration, higher estimated glomerular filtration rate, and unfavorable patient background characteristics, such as dyslipidemia, higher body mass index (BMI), and higher level of hemoglobin A1c.

**Effect of ipragliflozin on liver function**

The effect of ipragliflozin on liver function was assessed in the efficacy analysis set at 3 months. The time course of changes in liver function-related parameters in all patients and in patients stratified by liver func-
tion status is shown in Figs. 2 and 3, respectively. In the overall patient population, the levels of AST, ALT, γ-GTP, and ALP decreased significantly from baseline to 1 and 3 months (Fig. 2). When patients were stratified by liver function status, statistically significant differences were observed at 3 months compared with baseline in both normal and abnormal liver function groups. However, a progressive decrease from 1 to 3 months was observed in the abnormal liver function group only (Fig. 3).

The time course change in the fatty liver index of all patients is shown in Fig. 4. The fatty liver index decreased significantly from 63.2677 ± 26.4363 at baseline to 56.7137 ± 27.6484 at 3 months (change: –6.7778 ± 9.7286, \( p < 0.05 \) vs. baseline) in the overall patient population. Among patients with abnormal liver function, the proportion of patients whose liver function normalized (ALT ≤30 [male] or ≤20 [female]) at 1 and 3 months was 13.8% (259/1,880) and 20.5% (543/2,648), respectively. The proportion of patients with unchanged or worsening liver function was 86.2% (1,621/1,880) and 79.5% (2,105/2,648) at 1 and 3 months, respectively.

The correlations between changes in ALT and changes in efficacy/laboratory parameters from baseline to 3 months are shown in Table 2. Among the overall patient population, there was no obvious correlation between the changes in ALT and changes in efficacy/laboratory parameters.

### Discussion

The present subgroup analysis of the STELLA-LONG TERM study was performed to evaluate the effect of ipragliflozin on liver function in Japanese T2DM patients, focusing on data collected up to 3 months. Patients were divided into two groups according to their liver function status at baseline.

There were several statistically significant differences in patient background characteristics between patients with normal and abnormal liver function status. There was a greater proportion of younger, female patients and a shorter duration of diabetes in the abnormal vs. normal liver function group. As expected, those in the abnormal liver function group had less favorable patient background characteristics, in terms of poor glycemic control and worse lipid profile, compared with those in the normal liver function group.

In the overall patient population of the present subgroup analysis, all liver function parameters improved significantly from baseline to 3 months. Decreases were observed in AST, ALT, and γ-GTP levels: –3.4, –5.8, and –9.4 U/L, respectively, at 3 months. These findings were comparable to the changes in AST, ALT, and γ-GTP levels (–2.4, –5.8, and –11.3 U/L, respectively) previously reported in a pooled analysis of five randomized controlled trials in patients treated with ipragliflozin [10]. Furthermore, the decrease in ALP (–8.9 U/L) observed in our study is in line with the findings of Kawata et al. [24], who reported a –11.4 U/L change in ALP at
### Table 1  Patient characteristics at baseline

| Efficacy analysis set | Normal liver function | Abnormal liver function | Test* | p-value | Unknown |
|-----------------------|------------------------|-------------------------|-------|---------|---------|
| Total, n (%)          | 2,570 (100.0)          | 3,239 (100.0)           |       |         | 2,824 (100.0) |
| Sex, n (%)            |                        |                         |       |         |         |
| Male                  | 1,761 (68.5)           | 1,808 (55.8)            | 1     | <0.001  | 1,722 (61.0) |
| Female                | 809 (31.5)             | 1,431 (44.2)            | 1     | <0.001  | 1,102 (39.0) |
| Age, n                |                        |                         | 2     | <0.001  |         |
| Mean ± SD, years      | 59.3 ± 11.5            | 53.5 ± 11.9             |       | 56.9 ± 11.9 |
| <65 years old, n (%)  | 1,662 (64.7)           | 2,612 (80.6)            | 1     | <0.001  | 2,072 (73.4) |
| ≥65 years old, n (%)  | 908 (35.3)             | 627 (19.4)              |       | 752 (26.6) |
| Unknown, n (%)        | 0 (0.0)                | 0 (0.0)                 |       | 0 (0.0)  |
| Body weight, n        |                        |                         | 2     | <0.001  |         |
| Mean ± SD, kg         | 74.43 ± 15.17          | 82.49 ± 18.24           |       | 77.54 ± 16.52 |
| Body mass index, n    | 2,021                  | 2,602                   | 2     | <0.001  | 1,404 |
| Duration of diabetes, n| 1,756                  | 2,368                   | 2     | <0.001  | 1,733 |
| Mean ± SD, years      | 9.453 ± 7.047          | 7.200 ± 5.860           |       | 7.614 ± 6.315 |
| <5, n (%)             | 490 (19.1)             | 918 (28.3)              | 1     | <0.001  | 668 (23.7) |
| ≥5 to <10, n (%)      | 478 (18.6)             | 783 (24.2)              |       | 497 (17.6) |
| ≥10 to <15, n (%)     | 416 (16.2)             | 404 (12.5)              |       | 341 (12.1) |
| ≥15, n (%)            | 372 (14.5)             | 263 (8.1)               |       | 227 (8.0) |
| Unknown, n (%)        | 814 (31.7)             | 871 (26.9)              |       | 1,091 (38.6) |
| Complications, n (%)  |                        |                         | 1     | <0.001  |         |
| No                    | 308 (12.0)             | 282 (8.7)               |       | 743 (26.3) |
| Yes                   | 2,255 (87.7)           | 2,945 (90.9)            |       | 2,048 (72.5) |
| Unknown               | 7 (0.3)                | 12 (0.4)                |       | 33 (1.2)  |
| Type of complication*, n (%) |
| Diabetic neuropathy   | 291 (11.3)             | 282 (8.7)               |       | 205 (7.3) |
| Diabetic nephropathy  | 541 (21.1)             | 621 (19.2)              |       | 327 (11.6) |
| Diabetic retinopathy  | 286 (11.1)             | 268 (8.3)               |       | 183 (6.5) |
| Cardiovascular disease, cerebrovascular disease | 320 (12.5) | 210 (6.5) | 204 (7.2) |
| Myocardial infarction | 51 (2.0)               | 34 (1.0)                |       | 31 (1.1) |
| Angina pectoris       | 143 (5.6)              | 92 (2.8)                |       | 80 (2.8) |
| Heart failure         | 66 (2.6)               | 49 (1.5)                |       | 41 (1.5) |
| Arteriosclerosis obliterans | 37 (1.4) | 24 (0.7) | 36 (1.3) |
| Cerebrovascular disease | 88 (3.4)           | 49 (1.5)                |       | 61 (2.2) |
### Table 1  Cont.

| Efficacy analysis set                          | Normal liver function | Abnormal liver function | Test | p-value | Unknown |
|------------------------------------------------|-----------------------|-------------------------|------|---------|---------|
| Hypertension                                   | 1,475 (57.4)          | 1,945 (60.0)            |      |         | 1,371 (48.5) |
| Dyslipidemia (hyperlipidemia)                  | 1,721 (67.0)          | 2,382 (73.5)            |      |         | 1,386 (49.1) |
| Osteoporosis                                   | 53 (2.1)              | 41 (1.3)                |      |         | 41 (1.5) |
| Hyperuricemia                                  | 242 (9.4)             | 378 (11.7)              |      |         | 170 (6.0) |
| Urinary tract infection                        | 2 (0.1)               | 8 (0.2)                 |      |         | 6 (0.2) |
| Genital infection                              | 2 (0.1)               | 3 (0.1)                 |      |         | 1 (0.0) |
| Malignant tumor                                | 17 (0.7)              | 21 (0.6)                |      |         | 17 (0.6) |
| Others                                         | 900 (35.0)            | 1,483 (45.8)            |      |         | 717 (25.4) |

**Estimated glomerular filtration rate, n**

|                          | Mean ± SD, mL/min/1.73 m² |
|--------------------------|---------------------------|
| Hypertension              | 79.86 ± 21.63             |
| Dyslipidemia (hyperlipidemia) | 84.70 ± 21.11             |

**HbA1c, n (%)**

|                          | Mean ± SD, mmHg |
|--------------------------|-----------------|
| Hypertension              | 133.0 ± 15.0    |
| Dyslipidemia (hyperlipidemia) | 133.7 ± 15.2    |

**Systolic blood pressure, n**

|                          | Mean ± SD, mmHg |
|--------------------------|-----------------|
| Hypertension              | 76.9 ± 10.6     |
| Dyslipidemia (hyperlipidemia) | 79.8 ± 11.0     |

**Diastolic blood pressure, n**

|                          | Mean ± SD, mmHg |
|--------------------------|-----------------|
| Hypertension              | 2,277           |
| Dyslipidemia (hyperlipidemia) | 2,848           |

**Low-density lipoprotein cholesterol, n**

|                          | Mean ± SD, mg/dL |
|--------------------------|------------------|
| Hypertension              | 2,064            |
| Dyslipidemia (hyperlipidemia) | 2,553           |

**High-density lipoprotein (HDL) cholesterol, n**

|                          | Mean ± SD, mg/dL |
|--------------------------|------------------|
| Hypertension              | 112.9 ± 31.6     |
| Dyslipidemia (hyperlipidemia) | 115.6 ± 32.2     |

**Non-HDL cholesterol, n**

|                          | Mean ± SD, mg/dL |
|--------------------------|------------------|
| Hypertension              | 1,213            |
| Dyslipidemia (hyperlipidemia) | 2,752           |

**Triglycerides, n**

|                          | Mean ± SD, mg/dL |
|--------------------------|------------------|
| Hypertension              | 2,253            |
| Dyslipidemia (hyperlipidemia) | 2,860           |

**Uric acid, n**

|                          | Mean ± SD, mg/dL |
|--------------------------|------------------|
| Hypertension              | 2,025            |
| Dyslipidemia (hyperlipidemia) | 2,513           |

**Hematocrit, n**

|                          | Mean ± SD, %     |
|--------------------------|------------------|
| Hypertension              | 42.45 ± 4.30     |
| Dyslipidemia (hyperlipidemia) | 43.72 ± 4.09     |

**AST, n**

|                          | Mean ± SD, U/L   |
|--------------------------|------------------|
| Hypertension              | 2,327            |
| Dyslipidemia (hyperlipidemia) | 2,985           |

**ALT, n**

|                          | Mean ± SD, U/L   |
|--------------------------|------------------|
| Hypertension              | 19.2 ± 5.2       |
| Dyslipidemia (hyperlipidemia) | 39.0 ± 21.8     |

**γ-GTP (Male), n**

|                          | Mean ± SD, U/L   |
|--------------------------|------------------|
| Hypertension              | 1,468            |
| Dyslipidemia (hyperlipidemia) | 1,565           |

**γ-GTP (Female), n**

|                          | Mean ± SD, U/L   |
|--------------------------|------------------|
| Hypertension              | 42.9 ± 38.7      |
| Dyslipidemia (hyperlipidemia) | 90.3 ± 102.2    |

**Mean ± SD, U/L**

|                          | Mean ± SD, U/L   |
|--------------------------|------------------|
| Hypertension              | 25.6 ± 22.5      |
| Dyslipidemia (hyperlipidemia) | 57.3 ± 58.8    |

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*1) Chi-squared test, 2) Two-sample t-test

*Some patients had more than one complication.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GTP, gamma-glutamyltransferase; HbA1c, hemoglobin A1c; SD, standard deviation
12 weeks after initiation of ipragliflozin therapy in the multicenter ASSIGN-K trial patient population.

A clinically significant improvement in liver function parameters was only observed in the subgroup with abnormal liver function. Although statistically significant differences were observed in AST, ALT, γ-GTP, and ALP levels from baseline to 1 and 3 months in the normal liver function group, these differences were not clinically significant. Improvements in liver-related parameters have also been reported with the use of other SGLT2 inhibitors. Significant decreases in AST, ALT, and γ-GTP levels from baseline to 3 months (12 weeks) were reported in T2DM patients with NASH treated with dapagliflozin [25]. In a pooled subgroup analysis of two clinical trials of Japanese T2DM patients with high ALT level (>30 U/L), decreases in mean ALT levels were

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**Fig. 2** Time course changes in liver function-related parameters in the overall patient population. *p < 0.05 vs. baseline (paired t-test)

Abbreviations: ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; γ-GTP, gamma-glutamyltransferase; SD, standard deviation
observed: $-10.3 \pm 11.7$ U/L at 3 months (12 weeks) in patients treated with canagliflozin [26]. A retrospective study of T2DM patients who were treated with SGLT2 inhibitors, including ipragliflozin, dapagliflozin, luseogliflozin, canagliflozin, tofogliflozin, and empagliflozin, reported a significant decrease in AST and ALT levels after 3 months of treatment [27]. In that study, the decrease in ALT levels was significantly correlated with the ALT level at baseline. Our findings together with those of previous studies on other SGLT2 inhibitors

![Graph showing changes in liver function-related parameters over time for patients stratified by liver function status](image)

**Fig. 3** Time course changes in liver function-related parameters in patients stratified by liver function status. *p < 0.05 vs. baseline (paired t-test)

Abbreviations: ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; y-GTP, gamma-glutamyltransferase; SD, standard deviation
suggest the usefulness of SGLT2 inhibitors for improving liver function in T2DM patients, particularly in those with abnormal liver function.

In the present study, ALP levels decreased in both the normal and abnormal liver function groups. ALP is present in distinct forms in tissues other than the liver, such as the bones, small intestine, and placenta [28]. Because data according to the type of isozyme were not collected in this study, it is difficult to speculate on the reason for this finding.

In the present subgroup analysis, a significant improvement in the fatty liver index was shown from baseline to 3 months (−6.7778 ± 9.7286, p < 0.05). This finding is consistent with that of another study in which Japanese T2DM patients who were treated with ipragliflozin showed a decrease in fatty liver index from 70.1 ± 19.4 at baseline to 60.3 ± 25.5 at 4 months (16 weeks) (mean change −9.8 ± 6.1) [29]. This improvement in fatty liver index supports the findings of a recent study that reported a decrease in hepatic and visceral fat in Japanese T2DM patients treated with ipragliflozin [30]. The relationship between ipragliflozin therapy and changes in visceral fat should be investigated in future studies as this parameter was not evaluated in the present subgroup analysis. Decreases in visceral fat have also been suggested to be predictors of NAFLD [31].

### Table 2  Correlation between changes in ALT and changes in efficacy/laboratory parameters at 3 months in the overall patient population

|                         | n   | r (Pearson) | p-value (Pearson) |
|-------------------------|-----|-------------|-------------------|
| Changes in HbA1c (NGSP)| 4,689| 0.197       | <0.001            |
| Changes in fasting plasma glucose| 2,746| 0.140| <0.001 |
| Changes in fasting insulin| 218| −0.153| 0.024 |
| Changes in body weight| 3,921| 0.203| <0.001 |
| Changes in waist circumference| 763| 0.086| 0.018 |
| Changes in systolic blood pressure| 4,096| 0.026| 0.092 |
| Changes in diastolic blood pressure| 4,093| 0.054| <0.001 |
| Changes in total bilirubin| 2,023| 0.090| <0.001 |
| Changes in triglycerides| 4,384| 0.076| <0.001 |

Abbreviations: ALT, alanine aminotransferase; HbA1c, hemoglobin A1c; NGSP, National Glycohemoglobin Standardization Program
liver index is a surrogate marker of NAFLD [32], which is relatively common in T2DM patients. This algorithm was developed as a simple, non-invasive, and less expensive method than imaging tests to predict NAFLD. Our findings suggest that ipragliflozin has the potential to reduce the risk of NAFLD in T2DM patients. In fact, a recent randomized study comparing the efficacy of ipragliflozin vs. pioglitazone in T2DM patients with NAFLD reported similar beneficial effects on NAFLD and glycemic control with both drugs [33].

No obvious correlation was found between the changes in ALT and the changes in efficacy/laboratory parameters at 3 months. A possible reason for this finding may be that the present correlation analysis included the overall patient population regardless of their liver function status at baseline. We plan to conduct further correlation analyses in a larger sample size and only in patients with abnormal liver function to explore factors affecting the improvement of liver function.

The limitations of the study included potential bias from incorrect completion of the report forms, lack of liver function data for 2,824 patients, and lack of an active control group for comparisons. As this is a single-cohort, exploratory surveillance study, the results of statistical tests should be interpreted accordingly. The results of this interim report should be considered preliminary in nature, as more data will be collected, and results of further interim and final analyses will become available in the future.

In conclusion, ipragliflozin treatment for 3 months improved liver function parameters in T2DM patients with abnormal liver function at baseline; no clinically significant changes were observed in patients with normal liver function at baseline. Further study is warranted to identify possible factors associated with the improvements in patients with abnormal liver function.

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Author Contributions

Tabuchi H contributed to the study design, data collection, data analysis, and writing of the manuscript. Maegawa H, Tobe K, and Uno S contributed to the study design, data analysis, and writing of the manuscript. Nakamura I contributed to the study design, study conduct, data analysis, and writing of the manuscript.

Disclosure Statement

Ichiro Nakamura, Hiromi Tabuchi, and Satoshi Uno are employees of Astellas Pharma Inc.

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