Effect of ipragliflozin on liver function in Japanese type 2 diabetes mellitus patients: subgroup analysis of a 3-year post-marketing surveillance study (STELLA–LONG TERM)

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Abstract. The STELLA-LONG TERM prospective post-marketing surveillance study assessed ipragliflozin in Japanese patients with type 2 diabetes mellitus (T2DM). This subgroup analysis of patients with liver impairment used the final 3-year results. Data on patients, adverse drug reactions (ADRs), and changes in glycemic parameters and liver enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma-glutamyl transpeptidase [γ-GTP] and alkaline phosphatase [ALP]) were collected, and the fatty liver index (FLI) was calculated. In the effectiveness analysis (n = 8,763), baseline liver function was normal in 2,605 patients (ALT <31/<21 U/L [men/women]) and abnormal in 3,277 (ALT ≥31/≥21 U/L). The abnormal liver function group had higher mean body weight and BMI than the normal liver function group (p < 0.001). In the safety analysis (n = 11,051), urinary tract infections, genital infections and hepatic disorders were more common in the abnormal than normal liver function group (2.25% vs. 1.07%; 1.78% vs. 1.14% and 1.85% vs. 1.01%). In the abnormal liver function group, there were significant (p < 0.001) decreases from baseline at 36 months in AST and ALT (from 38.8 and 53.7 U/L to 29.3 and 37.7 U/L, respectively), γ-GTP (from 75.4 to 51.7 U/L) and ALP (from 254.8 to 234.5 U/L), which were greater than in the normal liver function group. FLI reductions at 36 months were significant (p < 0.001) in subgroups with baseline FLI of ≥30 or ≥60. In conclusion, ipragliflozin improved liver function over 3 years in patients with impaired liver function, although ADRs occurred more frequently than in the normal liver function group.

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

IPRAGLIFLOZIN is a sodium–glucose cotransporter 2 (SGLT2) inhibitor that, in 2014, was approved for the treatment of type 2 diabetes mellitus (T2DM) in Japan [1]. SGLT2 inhibitors reduce serum glucose levels by stimulating urinary excretion of glucose, and are associated with reductions in blood pressure, triglycerides, and body weight [2]. Large cardiovascular outcomes trials have also indicated that SGLT2 inhibitors may provide cardiorenal protective effects among T2DM patients with cardiovascular or chronic kidney disease [3, 4], although these studies did not include Asian patients with T2DM [2]. According to the Japanese clinical practice guidelines, SGLT2 inhibitors should be considered in patients with T2DM who do not achieve glycemic targets with diet and lifestyle modifications [5].

Fat accumulation in the liver (simple hepatic steatosis) of a patient with T2DM likely signals the presence of non-alcoholic fatty liver disease (NAFLD), given that T2DM is a well-established risk factor for NAFLD [6], and that NAFLD is common in patients with T2DM (present in 55% of T2DM patients globally [7] and in 20–25% in Japan [8]). If the incidence of obesity and T2DM continue to increase at current rates, the prevalence of both NAFLD and non-alcoholic steatohepatitis (NASH) may be expected to increase [9]. This presents a significant public health concern, given that the diagnosis of NAFLD in patients with T2DM is associated with...
a higher prevalence of cardiovascular disease [10], and an increased risk of overall death [11].

In animal models of diabetes with comorbid obesity, hepatic steatosis and/or hepatic inflammation and fibrosis [12-16], chronic ipragliflozin administration improved not only hyperinsulinemia and hyperglycemia, but also obesity, hepatic steatosis, liver inflammation/oxidative stress, hepatic lipid content and liver fibrosis. These preclinical findings are supported by short-term (≤24-week) clinical studies demonstrating improvements in liver function or fatty liver in patients with T2DM treated with ipragliflozin [17-20]. A recent meta-analysis provided further evidence that treatment with SGLT2 inhibitors improves liver structure and function in patients with T2DM [21]. SGLT2 inhibition is a promising pharmacological approach for the treatment of NAFLD in patients with T2DM.

STELLA-LONG TERM is a 3-year prospective post-marketing surveillance study designed to evaluate the safety and effectiveness of ipragliflozin in Japanese patients with T2DM over an extended period of time [22]. Previous subgroup analyses of STELLA-LONG TERM conducted at 3 months have shown that ipragliflozin was associated with consistent decreases in liver enzymes, as well as in fatty liver index (FLI), in patients who had abnormal liver function at baseline (normal [FLI <30], abnormal [FLI ≥30] or fatty [FLI ≥60]). In addition, the proportion of patients with abnormal liver function at baseline whose liver function normalized (defined as ALT <31 U/L in men or <21 U/L for women) and those with abnormal liver function (defined as baseline ALT ≥31 U/L for men or ≥21 U/L for women).

Materials and Methods

Study design

The design of this study has been described in detail in previous publications [22, 23]. Briefly, this was an observational, multicenter, post-marketing surveillance study that was conducted in Japan (ClinicalTrials.gov identifier: NCT02479399).

Patient recruitment

All patients with T2DM who were first prescribed ipragliflozin between 17 July 2014 and 16 October 2015 at participating centers were included. Patients who had hepatitis B or hepatitis C were not excluded from this subgroup analysis. Each patient was followed over a 3-year period.

Treatment

In accordance with the prescribing information, patients received ipragliflozin 50 mg once daily, before or after breakfast. The prescribing information allows ipragliflozin to be administered at a lower dose; caution, and use of a lower dose, is advised in patients with hepatic impairment. The dose of ipragliflozin could also be increased to 100 mg in case of insufficient effectiveness, provided patients were closely monitored. All treatment decisions were made at the attending physician’s discretion.

Subgroups by baseline liver function

For this analysis, patients were divided into two subgroups: those with normal liver function (defined as baseline alanine aminotransferase [ALT] <31 U/L for men or <21 U/L for women) and those with abnormal liver function (defined as baseline ALT ≥31 U/L for men or ≥21 U/L for women).

Data collection and variables

Data on demographic and clinical characteristics, medication, laboratory variables, vital signs (blood pressure and heart rate) and safety (adverse drug reactions [ADRs]) were collected. Changes in aspartate aminotransferase (AST), ALT, gamma-glutamyl transpeptidase (γ-GTP), and alkaline phosphatase (ALP) levels and FLI in patients with normal and abnormal liver function were compared. FLI was calculated as described by Bedogni and colleagues [24]. Changes in FLI over the course of the study were also analyzed in patients according to FLI at baseline (normal [FLI <30], abnormal [FLI ≥30] or fatty [FLI ≥60]). In addition, the proportion of patients with abnormal liver function at baseline whose liver function normalized (defined as ALT <31 U/L in men or <21 U/L in women) after 3 years of treatment with ipragliflozin, and correlations between changes in ALT levels and effectiveness variables/laboratory values were evaluated. Finally, correlations between changes in ALT levels and changes in effectiveness and laboratory parameters were analyzed in patients according to baseline body mass index (BMI) category (<22 kg/m², ≥22 to <25 kg/m², ≥25 to <30 kg/m², ≥30 to <35 kg/m² or ≥35 kg/m²). Patients with abnormal liver function were included in the correlation analysis.

Statistical analysis

Sample size calculations and the choice of follow-up duration have been described in a prior publication [22]. No sample size calculations were performed for the subgroup comparisons. Quantitative variables (including vital signs, effectiveness and laboratory variables) were summarized as means ± standard deviations (SD). Paired t-tests were used to assess changes from baseline. Qualitative variables (including baseline characteristics) were summarized as n (%). Patient characteristics and effectiveness parameters were compared between the two groups using the two-sample t-test and chi-squared test. No adjustments for type-I error based on multiple
hypothesis testing were performed in the present sub-
group analysis. Pearson’s correlation coefficient was cal-
culated to evaluate the relationship between changes in
ALT and changes in effectiveness/laboratory parameters.
All statistical calculations were performed using SAS
version 9.4 (SAS Institute Inc., Cary, North Carolina,
USA).

Ethics
This surveillance study complied with Japanese Good
Postmarketing Study Practice regulations. Because the
present study collected anonymized clinical data,
informed consent was not required.

Results

Patient disposition
A total of 11,424 patients treated at 2,431 medical
institutions were registered. Case report forms were col-
lected from 11,289 patients. Overall, 11,051 patients
were included in the safety analysis set while the effecti-
veness analysis set included 8,763 patients. Full details
of the overall safety and effectiveness analysis sets have
been reported in the final publication of results from this
study [25].

Patient characteristics
At baseline, 2,605 of the patients included in the effecti-
veness analysis set had normal liver function and 3,277
had abnormal liver function; liver function was unknown
in 2,881 patients.

There were several significant differences in demo-
graphic characteristics between patients with normal and
abnormal liver function in the effectiveness analysis set
(Table 1). Compared with patients with normal liver
function, patients with abnormal liver function had a
lower mean age (53.5 vs. 59.3 years, \( p < 0.001 \)), higher
mean body weight (82.49 vs. 74.24 kg, \( p < 0.001 \)),
higher mean BMI (30.63 vs. 27.56 kg/m², \( p < 0.001 \)), and
shorter mean duration of diabetes (7.17 vs. 9.43 years, \( p
< 0.001 \)) than those with normal liver function. Fewer
patients with abnormal liver function than those with
normal liver function were male (55.8% vs. 68.4% of
patients, \( p < 0.001 \)), had no complications (7.9% vs.
11.3%, \( p < 0.001 \)) or had glycated hemoglobin (HbA1c)
<8.0% (50.9% vs. 58.7%, \( p < 0.001 \)).

Safety
ADRs occurred in 2,129 of the 11,051 patients
(19.27%) and serious ADRs occurred in 210 patients
(1.90%; Table 2). The incidence of ADRs was signifi-
cantly higher in patients with abnormal liver function
(22.15%) than in patients with normal liver function
(19.74%, \( p = 0.014 \)). In contrast, the incidence of serious
ADRs was similar between patients with abnormal liver
function (1.96%) and patients with normal liver function
(2.24%, \( p = 0.414 \)). ADRs of special interest occurring
significantly more frequently in patients with abnormal
liver function than those with normal liver function
included urinary tract infections, genital infections and
hepatic disorders (2.25% vs. 1.07%, \( p < 0.001 \); 1.78% vs.
1.14%, \( p = 0.027 \) and 1.85% vs. 1.01%, \( p = 0.003 \),
respectively).

Effectiveness
Changes in AST, ALT, \( \gamma \)-GTP and ALP over the
course of the study are presented in Fig. 1. Statistically
significant changes in AST and ALT were observed at all
time points in patients with normal or abnormal liver
function at baseline (Figs. 1a and b). In patients with nor-
mal liver function, AST and ALT levels showed slight
but statistically significant increases from baseline (19.2
and 18.7 U/L, respectively) to 36 months (20.8 and 20.3
U/L, respectively; both \( p < 0.001 \) vs. baseline). However,
in patients with abnormal liver function, both AST and
ALT levels showed statistically significant decreases from
baseline (38.8 and 53.7 U/L, respectively) to 36 months
(29.3 and 37.7 U/L, respectively; both \( p < 0.001 \) vs.
baseline). Significant differences in AST and ALT
changes from baseline were detected between patients
with normal liver function and patients with abnormal
liver function at 36 months (+1.5 vs. –8.8 U/L and +1.6
U/L vs. –15.2 U/L, respectively) and at all other time
points (\( p < 0.001 \) for all).

Relative to baseline, statistically significant decreases
in \( \gamma \)-GTP levels were observed in patients with normal
liver function at all time points, except 36 months
(Fig. 1c). In patients with abnormal liver function, signif-
icant decreases in \( \gamma \)-GTP levels from baseline (75.4 U/L)
were observed at 36 months (51.7 U/L) and at all other
time points (\( p < 0.001 \) vs. baseline for all). Significant
differences in the change from baseline at 36 months in
\( \gamma \)-GTP levels were detected between patients with
normal liver function and patients with abnormal liver
function (–1.8 vs. –20.3 U/L), as well as the change from
baseline in this parameter at all other time points (\( p <
0.001 \) for all).

In patients with normal liver function, significant
decreases in ALP levels from baseline (232.8 U/L)
detected at 1 and 3 months only (222.1 and 227.1 U/L;
changes from baseline –11.4 and –3.5 U/L; \( p < 0.05 \) vs.
baseline for both), while in patients with abnormal liver
function, ALP levels were significantly decreased from
baseline (254.8 U/L) at 36 months (234.5 U/L; change
from baseline –16.3 U/L) and at all other time points
(\( p < 0.001 \) vs. baseline for all; Fig. 1d). Significant dif-
### Table 1  Baseline patient characteristics (effectiveness analysis set)

|                          | Normal liver function | Abnormal liver function | p-value | Unknown |
|--------------------------|-----------------------|-------------------------|---------|---------|
| **Total, n (%)**         | 2,605 (100.0)         | 3,277 (100.0)           |         | 2,881 (100.0) |
| **Sex, n (%)**           |                       |                         |         |         |
| Male                     | 1,782 (68.4)          | 1,827 (55.8)            | <0.001  | 1,760 (61.1) |
| Female                   | 823 (31.6)            | 1,450 (44.2)            |         | 1,121 (38.9) |
| **Age, n**               | 2,605                 | 3,277                   |         | 2,881 |
| Mean ± SD, <65, n (%)    | 59.3 ± 11.5           | 53.5 ± 11.9             | <0.001  | 56.9 ± 11.9 |
| ≥65, n (%)               | 1,683 (64.6)          | 2,647 (80.8)            | <0.001  | 2,108 (73.2) |
| **Body weight, n**       | 2,243                 | 2,889                   |         | 1,753 |
| Mean ± SD, kg            | 74.24 ± 15.15         | 82.49 ± 18.18           | <0.001  | 77.45 ± 16.38 |
| **BMI, n**               | 2,104                 | 2,716                   |         | 1,503 |
| Mean ± SD, <18.5, n (%)  | 27.56 ± 4.70          | 30.63 ± 5.44            | <0.001  | 28.78 ± 4.94 |
| ≥18.5 to <22.0, n (%)    | 7 (0.3)               | 6 (0.2)                 |         | 6 (0.2) |
| ≥22.0 to <25.0, n (%)    | 131 (5.0)             | 52 (1.6)                |         | 63 (2.2) |
| ≥25.0 to <30.0, n (%)    | 496 (19.0)            | 253 (7.7)               |         | 257 (8.9) |
| ≥30.0 to <35.0, n (%)    | 945 (36.3)            | 1,089 (33.2)            |         | 654 (22.7) |
| ≥35.0, n (%)             | 526 (20.1)            | 507 (15.5)              |         | 159 (5.5) |
| <25.0, n (%)             | 634 (24.3)            | 311 (9.5)               | <0.001  | 326 (11.3) |
| ≥25.0, n (%)             | 1,470 (56.4)          | 2,405 (73.4)            |         | 1,177 (40.9) |
| Unknown, n (%)           | 501 (19.2)            | 561 (17.1)              |         | 1,378 (47.8) |
| **Type of consultation, n (%)** |                       |                         |         |         |
| Hospitalization          | 53 (2.0)              | 81 (2.5)                | 0.264   | 20 (0.7) |
| Outpatient clinic        | 2,552 (98.0)          | 3,196 (97.5)            |         | 2,861 (99.3) |
| **Duration of diabetes, n** |                       |                         |         |         |
| Mean ± SD, years         | 9.43 ± 7.03           | 7.17 ± 5.84             | <0.001  | 7.62 ± 6.37 |
| <5, n (%)                | 496 (19.0)            | 931 (28.4)              | <0.001  | 684 (23.7) |
| ≥5 to <10, n (%)         | 477 (18.3)            | 793 (24.2)              |         | 503 (17.5) |
| ≥10 to <15, n (%)        | 427 (16.4)            | 405 (12.4)              |         | 344 (11.9) |
| ≥15, n (%)               | 373 (14.3)            | 264 (8.1)               |         | 233 (8.1) |
| Unknown, n (%)           | 832 (31.9)            | 884 (27.0)              |         | 1,117 (38.8) |
| **Complications, n (%)** |                       |                         |         |         |
| No                       | 295 (11.3)            | 260 (7.9)               | <0.001  | 704 (24.4) |
| Yes                      | 2,305 (88.5)          | 3,006 (91.7)            |         | 2,146 (74.5) |
| Unknown                  | 5 (0.2)               | 11 (0.3)                |         | 31 (1.1) |
| **Type of complicationa, n (%)** |                   |                         |         |         |
| Diabetic neuropathy      | 295 (11.3)            | 291 (8.9)               |         | 208 (7.2) |
| Diabetic nephropathy     | 559 (21.5)            | 639 (19.5)              |         | 337 (11.7) |
| Diabetic retinopathy     | 285 (10.9)            | 270 (8.2)               |         | 186 (6.5) |
| CV and cerebrovascular diseases | 359 (13.8)         | 248 (7.6)               |         | 231 (8.0) |
| Myocardial infarction    | 53 (2.0)              | 35 (1.1)                |         | 30 (1.0) |
| Angina pectoris          | 159 (6.1)             | 99 (3.0)                |         | 87 (3.0) |
| Heart failure            | 73 (2.8)              | 50 (1.5)                |         | 40 (1.4) |
| Arteriosclerosis obliterans | 46 (1.8)          | 29 (0.9)                |         | 43 (1.5) |
| Cerebrovascular disorder | 107 (4.1)             | 77 (2.3)                |         | 78 (2.7) |
Table 1  Cont.

| Condition                          | Normal liver function | Abnormal liver function | p-value\(^a\) | Unknown          |
|------------------------------------|-----------------------|-------------------------|---------------|-----------------|
| Hypertension                       | 1,521 (58.4)          | 1,999 (61.0)            |               | 1,422 (49.4)    |
| Dyslipidemia (hyperlipidemia)      | 1,774 (68.1)          | 2,454 (74.9)            |               | 1,479 (51.3)    |
| Osteoporosis                       | 55 (2.1)              | 49 (1.5)                |               | 42 (1.5)        |
| Gout and hyperuricemia             | 252 (9.7)             | 396 (12.1)              |               | 177 (6.1)       |
| Urinary tract infection            | 5 (0.2)               | 9 (0.3)                 |               | 7 (0.2)         |
| Genital infection                  | 2 (0.1)               | 4 (0.1)                 |               | 1 (0.0)         |
| Malignant tumor                    | 23 (0.9)              | 23 (0.7)                |               | 22 (0.8)        |
| Unknown                            | 951 (36.5)            | 1,580 (48.2)            |               | 812 (28.2)      |
| eGFR, n                             | 2,414                 | 2,945                   | (2) <0.001    | 266             |
| Mean ± SD, mL/min/1.73 m\(^2\)     | 79.06 ± 20.08         | 84.01 ± 19.51           |               | 77.74 ± 20.60   |
| HbA1c, n (%), <8.0%                 | 1,528 (58.7)          | 1,667 (50.9)            | (1) <0.001    | 1,671 (58.0)    |
|                                    | 1,071 (41.1)          | 1,603 (48.9)            |               | 1,186 (41.2)    |
| HbA1c, n (%), ≥8.0%                | 6 (0.2)               | 7 (0.2)                 |               | 24 (0.8)        |
| SBP, n                             | 2,373                 | 2,948                   |               | 1,823           |
| Mean ± SD, mmHg                    | 133.2 ± 15.1          | 133.8 ± 15.1            | (2) 0.135     | 132.7 ± 15.2    |
| DBP, n                             | 2,358                 | 2,904                   |               | 1,804           |
| Mean ± SD, mmHg                    | 76.9 ± 10.3           | 79.3 ± 10.3             | (2) <0.001    | 77.7 ± 10.6     |
| LDL cholesterol, n                 | 2,270                 | 2,790                   |               | 283             |
| Mean ± SD, mg/dL                   | 112.9 ± 31.3          | 115.8 ± 32.4            | (2) 0.001     | 114.8 ± 30.4    |
| HDL cholesterol, n                 | 2,349                 | 2,971                   |               | 260             |
| Mean ± SD, mg/dL                   | 52.6 ± 14.3           | 49.4 ± 12.7             | (2) <0.001    | 51.3 ± 14.4     |
| Non-HDL cholesterol, n             | 1,438                 | 1,823                   |               | 137             |
| Mean ± SD, mg/dL                   | 140.1 ± 35.7          | 146.2 ± 34.3            | (2) <0.001    | 144.1 ± 35.4    |
| Triglycerides, n                   | 2,464                 | 3,088                   |               | 302             |
| Mean ± SD, mg/dL                   | 177.1 ± 163.2         | 211.9 ± 200.6           | (2) <0.001    | 201.5 ± 142.7   |
| Uric acid, n                       | 2,235                 | 2,764                   |               | 178             |
| Mean ± SD, mg/dL                   | 5.22 ± 1.30           | 5.42 ± 1.32             | (2) <0.001    | 5.61 ± 1.46     |
| Hematocrit, n                      | 2,218                 | 2,674                   |               | 182             |
| Mean ± SD, %                       | 42.61 ± 4.08          | 43.82 ± 3.93            | (2) <0.001    | 43.01 ± 3.92    |
| AST, n                             | 2,566                 | 3,225                   |               | 22              |
| Mean ± SD, U/L                     | 19.2 ± 5.2            | 38.8 ± 21.7             | (2) <0.001    | 45.0 ± 42.5     |
| ALT, n                             | 2,605                 | 3,277                   |               | 0               |
| Mean ± SD, U/L                     | 18.7 ± 5.7            | 53.7 ± 30.9             | (2) <0.001    | —               |
| γ-GTP (male), n                    | 1,631                 | 1,693                   |               | 21              |
| Mean ± SD, U/L                     | 42.9 ± 38.6           | 90.1 ± 100.8            | (2) <0.001    | 61.7 ± 46.5     |
| γ-GTP (female), n                  | 742                   | 1,322                   |               | 13              |
| Mean ± SD, U/L                     | 25.6 ± 22.3           | 56.7 ± 57.2             | (2) <0.001    | 40.8 ± 30.9     |

\(^a\) P-values across subgroups assessed by (1) chi-squared test or (2) two-sample t-test; no statistical comparison between groups was made for specific complications.

\(^b\) Some patients had more than one complication.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CV, cardiovascular; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; γ-GTP, gamma-glutamyl transpeptidase; HbA1c, glycated hemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; SBP, systolic blood pressure; SD, standard deviation.
ferences in ALP changes from baseline were detected between patients with normal liver function and patients with abnormal liver function at 36 months (–3.6 vs. –16.3 U/L) and at all other time points, except at 1 month ($p < 0.001$).

FLI over the course of the study was analyzed in patients according to baseline FLI (Fig. 2). In patients with FLI <30 at baseline, significant decreases in FLI from baseline (19.4) were observed at 3, 6, 12, and 24 months (changes from baseline –3.4, –2.9, –2.7, and –2.7, respectively; $p < 0.05$ vs. baseline for all). In patients with FLI ≥30 and in patients with FLI ≥60, significant decreases in FLI from baseline (71.8 and 83.2, respectively) were observed at 36 months (change from baseline –11.5 and –11.8, respectively) and at all other time points ($p < 0.001$ for all).

Among patients with abnormal liver function at baseline, a continuous increase in the proportion of those whose ALT levels improved (defined as a decrease to <31 U/L for men and <21 U/L for women) was noted throughout the observational period (Table 3). While the proportion of patients whose ALT levels improved was 13.9% at 1 month, it further increased to 33.7% at 36 months.

In correlation analyses, where a moderate or high correlation in either direction ($r \geq 0.4$ or $r \leq –0.4$) that was also statistically significant ($p < 0.05$) was deemed a ‘significant correlation’, changes in ALT levels over the course of the study were not significantly correlated with most effectiveness and laboratory parameters in patients with abnormal liver function (Table 4).

Correlations between changes in ALT levels and changes in effectiveness and laboratory parameters were analyzed in patients according to baseline BMI (Table 5). There were no significant strong ($r \geq 0.4$ or $r \leq –0.4$) correlations between changes in ALT levels and changes in HbA1c, systolic blood pressure, diastolic blood pressure, low-density lipoprotein cholesterol levels or uric acid levels in any BMI subgroup. Although not significantly correlated, $r$ values for the correlation between ALT and HbA1c tended to increase with increasing baseline BMI in the ≥25 to <30 kg/m$^2$, ≥30 to <35 kg/m$^2$, and ≥35 kg/m$^2$ subgroups. There were significant strong correlations between changes in ALT levels and changes

### Table 2  Adverse drug reactions

|                           | Total ($n = 11,051$) | Normal liver function ($n = 3,371$) | Abnormal liver function ($n = 3,829$) | $p$-value | Unknown ($n = 4,051$) |
|---------------------------|----------------------|-------------------------------------|---------------------------------------|-----------|-----------------------|
| ADRs, $n$ (%)             | 2,129 (19.27)        | 626 (19.74)                         | 848 (22.15)                          | 0.014     | 655 (16.17)           |
| Serious ADRs              | 210 (1.90)           | 71 (2.24)                           | 75 (1.96)                            | 0.414     | 64 (1.58)             |
| ADRs of special interest  |                      |                                     |                                      |           |                       |
| Polyuria/pollakiuria       | 612 (5.54)           | 187 (5.90)                          | 245 (6.40)                           | 0.386     | 180 (4.44)            |
| Volume depletion-related event, including dehydration | 243 (2.20) | 69 (2.18) | 109 (2.85) | 0.076 | 65 (1.60) |
| Skin complication          | 198 (1.79)           | 55 (1.73)                           | 79 (2.06)                            | 0.318     | 64 (1.58)             |
| Renal disorder            | 191 (1.73)           | 59 (1.86)                           | 79 (2.06)                            | 0.544     | 53 (1.31)             |
| Urinary tract infection    | 170 (1.54)           | 34 (1.07)                           | 86 (2.25)                            | <0.001    | 50 (1.23)             |
| Genital infection         | 161 (1.46)           | 36 (1.14)                           | 68 (1.78)                            | 0.027     | 57 (1.41)             |
| Hepatic disorder          | 133 (1.20)           | 32 (1.01)                           | 71 (1.85)                            | 0.003     | 30 (0.74)             |
| Cardiovascular disease     | 67 (0.61)            | 25 (0.79)                           | 20 (0.52)                            | 0.166     | 22 (0.54)             |
| Hypoglycemia              | 57 (0.52)            | 21 (0.66)                           | 15 (0.39)                            | 0.115     | 21 (0.52)             |
| Malignant tumor           | 51 (0.46)            | 17 (0.54)                           | 16 (0.42)                            | 0.472     | 18 (0.44)             |
| Cerebrovascular disease    | 48 (0.43)            | 18 (0.57)                           | 18 (0.47)                            | 0.570     | 12 (0.30)             |
| Ketoacidosis, event related to ketone-body increase | 7 (0.06) | 3 (0.09) | 3 (0.08) | —$^b$ | 1 (0.02) |
| Fracture                  | 4 (0.04)             | 1 (0.03)                            | 2 (0.05)                             | —$^b$     | 1 (0.02)             |
| Lower limb amputation      | 0                    | 0                                   | 0                                     | —$^b$     | 0                     |

$^a$ $p$-values across subgroups assessed by chi-squared test.

$^b$ No $p$-value was calculated when at least one element of the contingency table was <10.

ADR, adverse drug reaction.
in body weight ($r = 0.446$, $p < 0.001$), BMI ($r = 0.442$, $p < 0.001$), and ALP levels ($r = 0.483$, $p = 0.008$) only in the subgroup of patients with baseline BMI of $<22$ kg/m$^2$. In contrast, correlations with changes in $\gamma$-GTP levels were significant and strong in all but the lowest ($<22$ kg/m$^2$) BMI subgroup ($r$ values of 0.403–0.470, all $p < 0.001$). Change in ALT levels were significantly correlated with changes in AST levels across all BMI subgroups (Table 5).

Correlations between the magnitude of change in FLI and changes in effectiveness and laboratory parameters were analyzed in patients according to FLI (Table 6). In all patients, including patients with abnormal or normal FLI, there were no significant correlations between

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Fig. 1  Time course changes in liver function-related parameters in patients stratified by liver function status at baseline. * $p < 0.001$, ** $p < 0.05$ vs. baseline (one-sample $t$-test); † $p < 0.001$ vs. patients with abnormal liver function (two-sample $t$-test).

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; $\gamma$-GTP, gamma-glutamyl transpeptidase; SD, standard deviation.
The present subgroup analysis of STELLA-LONG TERM was conducted to evaluate the safety of ipragliflozin and its effects on liver function over 3 years in Japanese patients with T2DM. The results of the safety analysis show that the incidence of ADRs was significantly higher in patients with abnormal liver function than in patients with normal liver function at baseline. Individual ADRs with significantly higher incidence among patients with abnormal liver function included urinary tract infections, genital infections and hepatic disorders. Risk factors for ipragliflozin-related ADRs, identified in the primary analysis of STELLA-LONG TERM [25], were more common in the patients with abnormal liver function in this analysis, and included female sex for urinary tract infections and genital infections, and the presence of any complications and mild/moderate hepatic impairment for hepatic disorders.

For the effectiveness analysis, patients were divided into those with normal liver function and those with abnormal liver function on the basis of ALT levels at baseline. In patients with abnormal liver function, continuous, statistically significant decreases in the levels of AST, ALT, γ-GTP, and ALP were observed throughout the study. In patients with normal liver function, changes in AST, ALT, γ-GTP, and ALP levels were also statistically significant at several time points, although they were numerically much smaller than changes observed in patients with abnormal liver function. Over the course of the study among patients who had abnormal liver function at baseline, the proportion whose liver function improved increased continuously from baseline, reaching

| Table 3 | Change in ALT levels in patients with abnormal liver function at baseline |
|---------|-----------------|
|         | 1 month | 3 months | 6 months | 12 months | 24 months | 36 months |
| Patients for whom ALT data were available, n (%) | 1,867 (100.0) | 2,645 (100.0) | 2,246 (100.0) | 2,154 (100.0) | 1,824 (100.0) | 1,601 (100.0) |
| ALT levels improved*, n (%) | 259 (13.9) | 542 (20.5) | 604 (26.9) | 663 (30.8) | 577 (31.6) | 540 (33.7) |
| ALT levels unchanged or worsened, n (%) | 1,608 (86.1) | 2,103 (79.5) | 1,642 (73.1) | 1,491 (69.2) | 1,247 (68.4) | 1,061 (66.3) |

* Improvement was defined as decrease to <31 U/L for men and <21 U/L for women.

ALT, alanine aminotransferase.

| Table 4 | Pearson’s correlation coefficients between changes in ALT and changes in effectiveness/laboratory parameters in patients with abnormal liver function |
|---------|---------------------------------|
|         | n     | r     | p-value |
| Changes in HbA1c | 1,581 | 0.166| <0.001 |
| Changes in FPG   | 888   | 0.096| 0.004  |
| Changes in fasting insulin | 66 | 0.059| 0.639  |
| Changes in body weight | 1,378 | 0.203| <0.001 |
| Changes in waist circumference | 259 | 0.056| 0.373  |
| Changes in SBP   | 1,435 | 0.062| 0.019  |
| Changes in DBP   | 1,413 | 0.078| 0.003  |
| Changes in total bilirubin | 683 | 0.102| 0.007  |
| Changes in triglycerides | 1,478 | 0.114| <0.001 |
| Changes in FLI   | 242   | 0.282| <0.001 |
| Changes in HOMA-IR | 16 | 0.543| 0.030  |

DBP, diastolic blood pressure; FLI, Fatty Liver Index; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; SBP, systolic blood pressure.

Discussion

The present subgroup analysis of STELLA-LONG TERM was conducted to evaluate the safety of ipragliflozin and its effects on liver function over 3 years in Japanese patients with T2DM. The results of the safety analysis show that the incidence of ADRs was significantly higher in patients with abnormal liver function than in patients with normal liver function at baseline. Individual ADRs with significantly higher incidence among patients with abnormal liver function included urinary tract infections, genital infections and hepatic disorders. Risk factors for ipragliflozin-related ADRs, identified in the primary analysis of STELLA-LONG TERM [25], were more common in the patients with abnormal liver function in this analysis, and included female sex for urinary tract infections and genital infections, and the presence of any complications and mild/moderate hepatic impairment for hepatic disorders.

For the effectiveness analysis, patients were divided into those with normal liver function and those with abnormal liver function on the basis of ALT levels at baseline. In patients with abnormal liver function, continuous, statistically significant decreases in the levels of AST, ALT, γ-GTP, and ALP were observed throughout the study. In patients with normal liver function, changes in AST, ALT, γ-GTP, and ALP levels were also statistically significant at several time points, although they were numerically much smaller than changes observed in patients with abnormal liver function. Over the course of the study among patients who had abnormal liver function at baseline, the proportion whose liver function improved increased continuously from baseline, reaching
Table 5  Pearson’s correlation coefficients between changes in effectiveness/laboratory parameters and changes in ALT in patients with abnormal liver function according to BMI at baseline

| Parameter                | BMI <22 kg/m²   | BMI ≥22 to <25 kg/m² | BMI ≥25 to <30 kg/m² | BMI ≥30 to <35 kg/m² | BMI ≥35 kg/m² |
|--------------------------|-----------------|-----------------------|-----------------------|-----------------------|---------------|
|                          | n   | r    | p-value | n   | r    | p-value | n   | r    | p-value | n   | r    | p-value | n   | r    | p-value |
| HbA1c                    | 55  | 0.223| 0.102   | 239 | 0.075| 0.248   | 1,032| 0.127| <0.001 | 787 | 0.253| <0.001 | 496 | 0.382| <0.001 |
| FPG                      | 35  | 0.136| 0.434   | 164 | 0.063| 0.425   | 622  | 0.043| 0.287  | 467 | 0.130| 0.005  | 293 | 0.250| <0.001 |
| Fasting insulin          | 5   | −0.944| −<0.001| 23  | −0.190| 0.386   | 69   | −0.046| 0.708  | 55  | 0.112| 0.417  | 33  | 0.137| 0.448  |
| Body weight              | 54  | 0.446| 0.001   | 229 | 0.110| 0.097   | 1,027| 0.221| <0.001 | 777 | 0.151| <0.001 | 487 | 0.220| <0.001 |
| Waist circumference      | 13  | 0.676| 0.011   | 60  | 0.044| 0.738   | 221  | −0.022| 0.750  | 177 | 0.003| 0.969  | 80  | 0.045| 0.691  |
| BMI                      | 54  | 0.442| <0.001  | 229 | 0.116| 0.081   | 1,027| 0.199| <0.001 | 777 | 0.149| <0.001 | 487 | 0.225| <0.001 |
| SBP                      | 55  | 0.091| 0.507   | 224 | 0.041| 0.542   | 970  | 0.016| 0.613  | 723 | 0.018| 0.626  | 456 | 0.154| <0.001 |
| DBP                      | 55  | 0.071| 0.607   | 221 | 0.127| 0.059   | 956  | 0.054| 0.096  | 709 | 0.029| 0.440  | 447 | 0.116| 0.014  |
| Heart rate               | 39  | 0.075| 0.652   | 140 | 0.075| 0.377   | 600  | 0.036| 0.379  | 454 | 0.109| 0.020  | 288 | 0.135| 0.022  |
| WBC                      | 50  | −0.104| 0.474  | 205 | −0.038| 0.584   | 851  | −0.034| 0.322  | 638 | 0.055| 0.167  | 391 | 0.049| 0.338  |
| RBC                      | 50  | −0.144| 0.318  | 206 | −0.008| 0.910   | 850  | 0.051| 0.137  | 639 | 0.089| 0.024  | 392 | 0.191| <0.001 |
| Hemoglobin               | 52  | −0.097| 0.495  | 207 | 0.046| 0.510   | 855  | 0.048| 0.160  | 633 | 0.113| 0.005  | 392 | 0.194| <0.001 |
| Hematocrit               | 49  | −0.072| 0.622  | 206 | 0.047| 0.505   | 850  | 0.020| 0.557  | 633 | 0.101| 0.011  | 394 | 0.157| 0.002  |
| AST                      | 57  | 0.750| <0.001  | 239 | 0.726| <0.001  | 1,017| 0.834| <0.001 | 777 | 0.843| <0.001 | 487 | 0.872| <0.001 |
| γ-GTP                    | 53  | 0.327| 0.017   | 220 | 0.458| <0.001  | 944  | 0.421| <0.001 | 743 | 0.470| <0.001 | 449 | 0.403| <0.001 |
| ALP                      | 29  | 0.483| 0.008   | 120 | 0.238| 0.009   | 572  | 0.110| 0.009  | 442 | 0.196| <0.001 | 264 | 0.267| <0.001 |
| Total bilirubin          | 28  | 0.284| 0.143   | 110 | −0.067| 0.490   | 451  | 0.090| 0.057  | 339 | 0.098| 0.071  | 200 | 0.308| <0.001 |
| Total cholesterol        | 34  | 0.026| 0.883   | 138 | 0.128| 0.134   | 619  | 0.051| 0.204  | 471 | 0.007| 0.879  | 290 | 0.150| 0.011  |
| LDL cholesterol          | 48  | −0.194| 0.187  | 215 | 0.046| 0.503   | 885  | 0.080| 0.018  | 669 | 0.019| 0.622  | 402 | 0.175| <0.001 |
| HDL cholesterol          | 49  | −0.006| 0.967  | 220 | 0.025| 0.714   | 950  | −0.108| <0.001 | 721 | −0.072| 0.054  | 452 | 0.008| 0.869  |
| Triglycerides            | 51  | 0.209| 0.141   | 230 | 0.007| 0.914   | 988  | 0.118| <0.001 | 745 | 0.054| 0.141  | 461 | 0.089| 0.056  |
| Uric acid                | 47  | −0.008| 0.955  | 190 | 0.020| 0.789   | 886  | 0.116| <0.001 | 674 | 0.018| 0.649  | 416 | 0.116| 0.018  |
| BUN                      | 43  | 0.129| 0.409   | 191 | −0.125| 0.884   | 865  | −0.061| 0.075  | 632 | −0.093| 0.019  | 395 | −0.089| 0.076  |
| Serum albumin            | 21  | −0.354| 0.115  | 91  | 0.223| 0.034   | 439  | −0.010| 0.827  | 330 | 0.062| 0.263  | 196 | −0.029| 0.685  |
Table 5  Cont.

|                     | BMI <22 kg/m² | BMI ≥22 to <25 kg/m² | BMI ≥25 to <30 kg/m² | BMI ≥30 to <35 kg/m² | BMI ≥35 kg/m² |
|---------------------|--------------|----------------------|----------------------|----------------------|--------------|
|                     | n  | r     | p-value   | n  | r     | p-value   | n  | r     | p-value   | n  | r     | p-value   |
| Serum creatinine    | 51 | 0.001 | 0.996     | 221 | -0.110 | 0.104     | 958 | -0.006 | 0.853     | 719 | -0.142 | <0.001     | 450 | -0.029 | 0.539     |
| Na                  | 38 | 0.032 | 0.846     | 157 | -0.094 | 0.241     | 687 | -0.110 | 0.004     | 517 | -0.010 | 0.022     | 310 | -0.093 | 0.102     |
| Cl                  | 37 | 0.048 | 0.778     | 154 | -0.076 | 0.349     | 672 | -0.133 | <0.001     | 500 | -0.174 | <0.001     | 301 | -0.119 | 0.040     |
| K                   | 43 | -0.222 | 0.152     | 170 | 0.053 | 0.492     | 730 | -0.014 | 0.705     | 554 | -0.026 | 0.545     | 333 | 0.069 | 0.212     |
| Ca                  | 15 | -0.130 | 0.645     | 42  | 0.236 | 0.132     | 212 | -0.008 | 0.910     | 151 | 0.047 | 0.565     | 105 | 0.110 | 0.263     |
| P                   | 9  | -0.452 | —         | 20  | -0.116 | 0.625     | 102 | -0.029 | 0.776     | 72  | 0.027 | 0.821     | 61  | -0.150 | 0.248     |
| Mg                  | 1  | —     | —         | 10  | 0.133 | 0.714     | 40  | 0.086 | 0.600     | 20  | 0.070 | 0.769     | 18  | -0.447 | 0.063     |
| Ketone bodies       | 3  | -0.817 | —         | 8   | -0.441 | —         | 21  | -0.077 | 0.739     | 14  | 0.011 | 0.970     | 15  | 0.350 | 0.201     |
| Fasting C-peptide   | 1  | —     | —         | 12  | 0.102 | 0.751     | 34  | 0.475 | 0.005     | 34  | 0.058 | 0.745     | 13  | -0.044 | 0.886     |
| eGFR                | 49 | -0.005 | 0.972     | 219 | 0.124 | 0.066     | 950 | 0.043 | 0.185     | 710 | 0.183 | <0.001     | 440 | 0.014 | 0.765     |
| pH                  | 19 | 0.324 | 0.175     | 111 | -0.050 | 0.601     | 523 | -0.055 | 0.206     | 420 | -0.080 | 0.101     | 251 | -0.232 | <0.001     |
| Urinary albumin     | 4  | 0.191 | —         | 28  | 0.217 | 0.267     | 107 | -0.069 | 0.480     | 74  | 0.153 | 0.192     | 45  | -0.044 | 0.774     |
| Urinary creatinine  | 2  | -1.000 | —         | 24  | 0.011 | 0.959     | 73  | -0.054 | 0.648     | 63  | 0.111 | 0.386     | 37  | 0.140 | 0.408     |
| C-peptide index     | 10 | -0.142 | 0.697     | 32  | 0.187 | 0.305     | 32  | -0.233 | 0.198     | 11  | 0.020 | 0.952     |
| Non-HDL cholesterol | 30 | -0.039 | 0.838     | 131 | 0.109 | 0.217     | 572 | 0.026 | 0.538     | 436 | 0.027 | 0.574     | 271 | 0.139 | 0.022     |
| Fatty Liver Index   | 12 | 0.684 | 0.014     | 55  | 0.324 | 0.016     | 213 | 0.323 | <0.001     | 166 | 0.157 | 0.044     | 73  | 0.042 | 0.726     |
| HOMA-IR             | 5  | -0.950 | —         | 22  | 0.075 | 0.740     | 69  | -0.062 | 0.614     | 55  | -0.018 | 0.895     | 33  | 0.069 | 0.704     |
| HOMA-β              | 5  | -0.950 | —         | 22  | 0.075 | 0.740     | 69  | -0.062 | 0.614     | 55  | -0.018 | 0.895     | 33  | 0.069 | 0.704     |

*No p-value was calculated when at least one element of the contingency table was <10.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; γ-GTP, gamma-glutamyl transpeptidase; HbA1c, glycated hemoglobin; HDL, high density lipoprotein; HOMA-β, homeostatic model assessment of β-cell function; HOMA-IR, homeostatic model assessment of insulin resistance; LDL, low density lipoprotein; RBC, red blood cells; SBP, systolic blood pressure; WBC, white blood cells.
33.7% at 3 years. In the 2-year results of STELLA-LONG TERM [26], the subgroup of patients with abnormal liver function showed a continuous decrease from baseline in AST, ALT, γ-GTP, and ALP levels. The present analysis demonstrates that this effect is maintained a further year after the start of ipragliflozin treatment. To the best of our knowledge, this is the first study in Japanese patients to demonstrate long-term benefit of ipragliflozin on liver function in this patient subpopulation.

After 1 month, ALP levels decreased both in patients with normal and in patients with abnormal liver function in the present study. Distinct forms of ALP are found in tissues other than the liver, including the bones, small intestine, and placenta [27]. In this study, we did not collect ALP data according to the type of isozyme, and therefore, it is difficult to speculate about the reason for this finding. Another possible reason is, as with the other parameters, mean changes in ALP from baseline were correlated with changes in AST regardless of BMI. Distinct forms might be assessed at each patient visit and, hence, it might lead to contradictory results between ALP values at the first and second months.

Our results confirm those from several previous studies in Japanese patients with T2DM, where ipragliflozin improved hepatic dysfunction [17], fatty liver [18, 19], and hepatic steatosis (liver-to-spleen attenuation ratio assessed using computed tomography) [28]. Where assessed, this improvement was independent of change in body weight [17, 19] or BMI [19]. One of these studies included 20 patients with T2DM receiving ipragliflozin 50 mg/day for 24 weeks; using magnetic resonance spectroscopy, study investigators demonstrated significant reductions from baseline in hepatic fat [18]. Collectively, these studies suggest ipragliflozin may have therapeutic efficacy in T2DM-associated hepatic steatosis. Other SGLT2 inhibitors have also been reported to improve liver function in T2DM [29-31]. In a pooled post-hoc analysis of canagliflozin studies in Japanese patients with T2DM, the subgroup of patients with impaired liver function (ALT >30 U/L) experienced improvements not only in glycemic parameters but also liver function and body weight [31]. While patients with impaired liver function were not examined specifically in an analysis of multiple clinical studies of empagliflozin in patients with T2DM, authors reported that the greatest reductions in ALT levels occurred in those in the highest tertile of ALT level at baseline, and that these reductions were generally independent of changes in body weight or HbA1c [30].

In our study, the changes in ALT levels in patients with abnormal liver function were not significantly correlated with changes in most effectiveness and laboratory parameters. They were significantly correlated with changes in body weight and BMI only in patients with a low BMI (BMI <22 kg/m²), i.e. were independent of BMI in most patients with abnormal liver function. As expected, changes in ALT were significantly correlated with changes in AST regardless of BMI.

For the effectiveness analysis, patients were also divided into those with normal (FLI <30), abnormal and fatty liver (FLI ≥30 and ≥60) on the basis of FLI at baseline. In this subgroup analysis, numerically greater decreases in FLI were observed in patients with abnormal or fatty FLI scores than in patients with normal liver FLI scores at baseline, and FLI scores decreased significantly from baseline in all subgroups. Prior subgroup analyses of ipragliflozin studies in Japanese patients with T2DM, which excluded patients in whom hepatic steatosis could be ruled out (i.e. baseline FLI <30) [19, 20], also found that FLI improved significantly from baseline after ipragliflozin treatment (from mean ± SD 64.5 ± 21.6 to 51.9 ± 26.5, p < 0.01 [20] and from 70.1 ± 19.4 to 60.3 ± 25.5, p = 0.0009 [19]). This improvement was correlated with changes in fasting plasma glucose levels.

### Table 6 Pearson’s correlation coefficients between changes in effectiveness/laboratory parameters and change in fatty liver index

|                  | Total                  | FLI normal (FLI <30) | FLI abnormal (FLI ≥30) |
|------------------|------------------------|----------------------|------------------------|
|                  | n  | r   | p-value | n  | r   | p-value | n  | r   | p-value |
| HbA1c            | 449 | 0.126 | 0.007   | 59  | 0.073 | 0.580   | 390 | 0.129 | 0.011   |
| FPG              | 350 | 0.146 | 0.006   | 53  | 0.224 | 0.106   | 297 | 0.130 | 0.026   |
| Fasting insulin  | 59  | 0.161 | 0.224   | 9   | –0.475 | 0.196   | 50  | 0.198 | 0.168   |
| SBP              | 446 | 0.153 | 0.001   | 59  | 0.000 | 1.000   | 387 | 0.154 | 0.002   |
| DBP              | 438 | 0.145 | 0.002   | 59  | 0.026 | 0.842   | 379 | 0.137 | 0.008   |
| Total bilirubin  | 279 | –0.087 | 0.147   | 39  | 0.205 | 0.210   | 240 | –0.103 | 0.112   |

DBP, diastolic blood pressure; FLI, Fatty Liver Index; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; SBP, systolic blood pressure.
in one of these analyses ($r = 0.4683, p = 0.0323$ [19]). However, our study did not confirm this correlation. In a previous, short-term study conducted by Takase et al., significant positive correlations were noted between the change in FLI and changes in FPG and HbA1c, while no significant correlation was detected between the change in FLI and changes in other parameters, including body weight and BMI [19]. These results contrast with the findings of the present study, in which no significant correlations were detected between the change in FLI and changes in any of the effectiveness or laboratory parameters analyzed. Two factors could have contributed to producing this difference in findings. First, in the study by Takase et al., ipragliflozin was administered for 16 weeks [19], while in the present study, it was administered for 3 years, which might be associated with the lack of correlation observed. Second, the study by Takase et al. included a total of 24 patients [19], while between 59 and 449 patients were included in the analysis of correlation between the change in FLI and changes in the effectiveness and laboratory parameters in the present study.

Several studies have identified ipragliflozin-related improvements in NAFLD parameters in addition to its favorable effect on glycemic parameters among Japanese patients with T2DM [32, 33], supporting our findings of a marked reduction in FLI and ALT levels in those with abnormal or fatty liver. In one of these studies [32], 24 weeks’ treatment increased the liver-to-spleen attenuation ratio, assessed via abdominal computed tomography, and significantly decreased HbA1c and ALT and fasting plasma glucose from baseline levels. In the control group treated with the thiazolidinedione pioglitazone [32], there were similar changes in these parameters compared with ipragliflozin. However, pioglitazone was associated with an increase in body weight whereas ipragliflozin gave a reduction in body weight (between-group difference $p < 0.0001$) [32]. In an ipragliflozin study that included patients with NAFLD or NASH [33], glycemic parameters and body weight were significantly reduced from baseline in both subgroups of patients, as were AST and ALT levels, indicating improvement in hepatic function. Significant reductions in $\gamma$-GTP, steatosis and a trend towards a reduction in liver stiffness were observed only in the NASH group [33]. Improvements in liver histopathology, including hepatic steatosis, and reductions in hepatic impairment among Japanese patients with both T2DM and NAFLD have been observed with other SGLT2 inhibitors as well, including dapagliflozin, canagliflozin and luseogliflozin [34-38].

It should be noted that there were significant differences in several baseline characteristics between patients with normal liver function and patients with abnormal liver function. More patients with abnormal liver function were aged <65 years and had a duration of diabetes of <5 years than patients with normal liver function. As would be expected, patients with normal liver function more frequently had no complications and adequate glycemic control than those with abnormal liver function.

This study had several limitations. Firstly, because this was a single-arm, observational study conducted in routine clinical practice, the safety findings and changes in laboratory parameters reported here could be affected by factors other than ipragliflozin (e.g., concomitant antidiabetic drugs). Additionally, a substantial proportion of patients in our study (33%) had unknown liver function status at baseline, and changes in laboratory parameters were not evaluated after patients completed or discontinued ipragliflozin treatment. This should be taken into account when interpreting the long-term effects of ipragliflozin on liver function.

**Conclusions**

The present subgroup analysis of STELLA-LONG TERM shows that, in Japanese patients with T2DM, ipragliflozin is associated with a continuous improvement in liver function over a 3-year period. The incidence of ADRs was higher in patients with abnormal liver function than in those with normal liver function.

**Acknowledgments**

The authors thank all the participants in this study. This study was funded by Astellas Pharma Inc. We would like to thank Georgii Filatov and Tracy Harrison of Springer Healthcare Communications who provided medical writing assistance. This medical writing assistance was funded by Astellas Pharma Inc.

**Disclosures**

Kazuyuki Tobe has received lecture fees from MSD K.K., Novo Nordisk Pharma Ltd., Kowa Pharmaceutical Co. Ltd. and grants from Daiichi Sankyo Co. Ltd., Ono Pharmaceutical Co. Ltd., Takeda Pharmaceutical Co. Ltd., Nippon Boehringer Ingelheim Co. Ltd., MSD K.K., Mitsubishi Tanabe Pharma Corporation, Teijin Pharma Limited, Eli Lily Japan K.K., Asahi Kasei Pharma Corporation, The Mitsubishi Foundation, and Suntory Global Innovation Center Ltd.; Hiroshi Maegawa has received lecture fees from MSD K.K., Sanofi K.K., Astellas Pharma Inc., Nippon Boehringer Ingelheim Co. Ltd., Takeda Pharmaceutical Co. Ltd., Mitsubishi Tanabe Pharma Corporation, Daiichi Sankyo Co. Ltd., Astra Zeneca K.K., Eli Lilly Japan K.K., Novo Nordisk
Pharma Ltd. and Sumitomo Dainippon Pharma Co. Ltd., research support from Astellas Pharma Inc., AstraZeneca K.K., Nippon Boehringer Ingelheim Co. Ltd., Sunstar Inc., Mitsubishi Tanabe Pharma Corporation, Kyowa Kirin Co. Ltd., Nissan Chemical Corporation and MIKI Corporation, and grants from Takeda Pharmaceutical Co. Ltd., Astellas Pharma Inc., MSD K.K., Nippon Boehringer Ingelheim Co. Ltd., Mitsubishi Tanabe Pharma Corporation, Daiichi Sankyo Co. Ltd., Sumitomo Dainippon Pharma Co. Ltd., Kowa Pharmaceutical Co. Ltd., Taisho Pharmaceutical Co. Ltd., Shionogi & Co. Ltd., Novartis Pharma K.K. and Nipro Corporation. Ichiro Nakamura and Satoshi Uno Limited, Shionogi & Co. Ltd., Novartis Pharma K.K. and Kyowa Kirin Co. Ltd., Nissan Chemical Corporation

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