Efficacy and safety of once-weekly semaglutide in Japanese individuals with type 2 diabetes in the SUSTAIN 1, 2, 5 and 9 trials: Post-hoc analysis

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**ABSTRACT**

**Aims/Introduction:** The etiology and treatment of type 2 diabetes might differ between specific populations. This post-hoc exploratory analysis assessed the efficacy and safety of once-weekly subcutaneous semaglutide vs comparators in Japanese individuals with type 2 diabetes in comparison with the total population from four phase III studies in the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN) program.

**Materials and Methods:** This analysis was carried out with data from the SUSTAIN 1, 2, 5 and 9 trials. Post-hoc analyses were carried out to assess outcomes in all participants and in Japanese participants in each study. The primary end-point was the change from baseline to end of study in glycated hemoglobin (%). The confirmatory secondary end-point was change from baseline to end of study in bodyweight (kg).

**Results:** Change from baseline to end of study in glycated hemoglobin with once-weekly semaglutide ranged from -1.32 to -1.85% points in the overall populations, and -1.69 to -2.49% points in Japanese participants. With once-weekly semaglutide, relative bodyweight was reduced from baseline to end of study by 4.0–7.3% in the overall populations, and 2.7–10.4% in Japanese participants. In the Japanese subpopulation, no new safety concerns were identified with once-weekly semaglutide, and there were no adverse events leading to death or severe hypoglycemic episodes.

**Conclusions:** In this post-hoc analysis, participants with type 2 diabetes initiating once-weekly semaglutide experienced improvements in glycated hemoglobin and bodyweight in both the overall and Japanese population, and no new safety concerns were identified among Japanese participants, supporting the efficacy of once-weekly semaglutide in this population.

**INTRODUCTION**

Differences between populations impact the etiology and treatment of type 2 diabetes\(^1\)–\(^3\). In East Asian populations, the development of type 2 diabetes is characterized by β-cell dysfunction, which is in contrast to the insulin resistance etiology more typical in Western populations\(^1\)–\(^3\). Type 2 diabetes also develops at a younger age and in individuals with a lower mean body mass index (BMI) compared with individuals of European descent\(^4\). Furthermore, differences in diet between East Asian and Western patients might influence the effectiveness of antihyperglycemic medications\(^5\). East Asian patients with type 2 diabetes typically have lower adiposity compared with those in Western populations\(^6\). The BMI of East Asian patients with type 2 diabetes is on average lower compared with that of patients with type 2 diabetes from Western populations\(^5\). This raises the concern that weight loss in elderly patients with type 2 diabetes who are already lean might result in frailty or sarcopenia.

Once-weekly subcutaneous semaglutide, a glucagon-like peptide-1 receptor analog, is approved for the treatment of type 2 diabetes in Japan\(^7\). For the approval of antihyperglycemic drugs in Japan, regulators require these agents to be evaluated in Japanese patients with type 2 diabetes. Here, we describe four studies from the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes.
(SUSTAIN) clinical trial program (SUSTAIN 1, 2, 5 and 9) that included Japanese individuals treated with once-weekly subcutaneous semaglutide. The aim of this post-hoc exploratory analysis was to assess the clinical effects of the efficacy and safety of once-weekly semaglutide vs comparators in Japanese individuals with type 2 diabetes in comparison with the total population using data from the SUSTAIN 1, 2, 5 and 9 trials.

**MATERIALS AND METHODS**

**Study design of SUSTAIN studies and participants**

The present analysis included four phase III studies from the SUSTAIN clinical development program (SUSTAIN 1, 2, 5 and 9) that included Japanese participants in the enrolled populations. The study design and end-points of these trials were similar and have been published previously. Briefly, each study investigated: once-weekly semaglutide vs placebo, as monotherapy in drug-naive patients, in SUSTAIN 1 (duration 30 weeks; NCT02054897); once-weekly semaglutide vs sitagliptin, as add-on therapy in patients receiving metformin with or without thiazolidinedione, in SUSTAIN 2 (duration 56 weeks; NCT01930188); once-weekly semaglutide vs placebo, as add-on therapy in patients receiving basal insulin with or without metformin, in SUSTAIN 5 (duration 30 weeks; NCT02305381); and once-weekly semaglutide vs placebo, as add-on therapy in patients receiving a sodium–glucose cotransporter 2 inhibitor with or without metformin, with or without sulfonylurea, in SUSTAIN 9 (duration 30 weeks; NCT03086330).

The participants included were aged ≥18 years or for Japan aged ≥20 years with type 2 diabetes who had a baseline glycated hemoglobin (HbA1c) 7.0–10.5%, and were receiving stable treatment (SUSTAIN 2, 5 and 9) or were treated with diet and exercise for 30 days before screening (SUSTAIN 1). The studies were carried out in compliance with the Declaration of Helsinki and the International Conference Harmonization Good Clinical Practice. Participants provided informed consent before the commencement of any study-related activities.

**Post-hoc analyses**

Data from SUSTAIN 1, 2, 5 and 9 were evaluated separately, and post-hoc exploratory analyses were carried out to compare outcomes for the Japanese participants with the overall populations in each study. The primary end-point in the SUSTAIN 1, 2, 5 and 9 studies was the change from baseline to end of study (EOS) in HbA1c (%). The confirmatory secondary end-point was change from baseline to EOS in bodyweight (kg). Other secondary end-points included the proportion of participants achieving HbA1c level <7% at EOS. Safety assessments report the incidence of adverse events (AEs), gastrointestinal AEs and hypoglycemic episodes.

**Statistical analysis**

The present post-hoc analysis was carried out to address whether the finding of a favorable treatment effect of semaglutide on change in HbA1c from baseline to EOS vs comparators in the overall populations of SUSTAIN 1, 2, 5 and 9 was also seen in the Japanese participants.

Details of statistical analyses for the overall populations have already been published. For this post-hoc analysis of SUSTAIN 1, 2, 5 and 9, when there were two placebo groups in the same study, these were pooled for the efficacy and safety evaluations. For each trial, the sample size was determined to ensure a sufficient overall power (at least 80%) to confirm the efficacy of semaglutide vs the comparator for both the change in HbA1c and change in bodyweight. For SUSTAIN 1, 2 and 5, continuous end-points assessed over time (change in HbA1c, bodyweight and BMI) were analyzed using a mixed model for repeated measurements, with treatment and stratification variables (for SUSTAIN 5) as fixed factors, and baseline value as the covariate, all nested within visits. In SUSTAIN 9, an analysis of covariance model with treatment and stratification variables as fixed factors and baseline value as the covariate was used, with multiple imputation carried out for missing data.

Efficacy evaluations were based on the full analysis set in the ‘on-treatment without rescue medication’ observation period, and safety assessments were based on the safety analysis set in the ‘on-treatment’ observation period.

**RESULTS**

**Participant disposition and baseline characteristics**

There were 2,310 participants in total over the SUSTAIN 1, 2, 5 and 9 studies, which included 312 Japanese participants. The majority of the baseline characteristics were generally similar in the overall populations and Japanese participants, with a mean age of 53.7–58.8 years and 52.4–58.8 years, mean diabetes duration of 4.2–13.3 years and 7.5–14.9 years, mean HbA1c of 8.0–8.4% and 8.2–8.4%, and mean fasting plasma glucose of 8.6–9.7 mmol/L and 7.0–9.1 mmol/L, respectively (Table 1). However, the mean BMI in the overall populations differed from that in Japanese participants, ranging from 31.9–32.9 kg/m² and 25.7–28.1 kg/m², respectively (Table 1).

**HbA1c**

Change from baseline to EOS in HbA1c with once-weekly semaglutide ranged from −1.32 to −1.85% points in the overall populations, and from −1.69 to −2.49% points in Japanese participants (Figure 1). These reductions tended to be greater among participants receiving a weekly semaglutide dose of 1.0 mg compared with 0.5 mg. There was a consistent trend in favor of once-weekly semaglutide vs comparator (placebo or sitagliptin) for the estimated treatment effects for change from baseline to EOS in all four studies, in the overall populations and in Japanese participants. This treatment effect tended to be slightly greater in the Japanese cohorts compared with the overall populations in all four studies. The proportion of participants reaching the HbA1c <7% target at EOS with once-weekly semaglutide was 61–79% in the overall populations and 71–100% in Japanese participants (Figure 2). The proportion of participants reaching HbA1c <7% tended to be higher among
| Demographics and baseline characteristics | SUSTAIN 1 | SUSTAIN 2 | SUSTAIN 5 | SUSTAIN 9 |
|------------------------------------------|----------|----------|----------|----------|
| n (FAS)                                  | 387      | 1,225    | 396      | 302      |
| Age (years)                              | 53.7 (11.3) | 55.1 (10.0) | 58.8 (10.1) | 58.8 (8.8) |
| Female, n (%)                            | 177 (45.7) | 605 (49.4) | 174 (43.9) | 126 (41.7) |
| Race, n (%)                              |          |          |          |          |
| White                                    | 249 (64.3) | 839 (68.5) | 307 (77.5) | 209 (69.2) |
| Asian                                    | 83 (21.4) | 307 (25.1) | 66 (16.7)  | 71 (23.5)  |
| Black or African American                | 31 (8.0)  | 59 (4.8)  | 21 (5.3)  | 13 (4.3)   |
| Native American or Alaska Native         | 1 (0.3) | 0 (0) | 0 (0) | 0 (0) |
| Native Hawaiian or other Pacific Islander| 0 (0) | 0 (0) | 1 (0.3) | 0 (0) |
| Other                                    | 23 (5.9) | 20 (1.6) | 0 (0) | 2 (0.7) |
| HbA1c (%)                                | 8.1 (0.9) | 8.1 (0.9) | 8.4 (0.8) | 8.0 (0.8) |
| Fasting plasma glucose (mmol/L)          | 9.7 (2.7)$^\dagger$ | 9.4 (2.3)$^\ddagger$ | 8.6 (3.0)$^\ddagger$ | 7.0 (2.2) |
| Bodyweight (kg)                          | 91.9 (23.8) | 89.5 (20.3) | 91.7 (21.0) | 91.7 (21.0) |
| Body mass index (kg/m²)                  | 32.9 (7.7) | 32.5 (6.2) | 32.2 (6.2) | 31.9 (6.6) |
| Diabetes duration (years)                | 42 (5.5)$^\ddagger$ | 66 (5.1) | 133 (7.8) | 97 (6.1) |
| eGFR (mL/min/1.73 m²)                    | 95.6 (7.6) | 97.5 (22.4) | 87.9 (288) | 95.2 (15.2) |

Data are mean (standard deviation) or number (proportion) of patients. Data are based on the ‘on-treatment without rescue medication’ observation period in the full analysis set (FAS).

$^\dagger$ Geometric mean shown. Total of four studies $n = 2,310$ (FAS). $^\ddagger n = 381$. $^\ddagger n = 1,164$. $^\ddagger n = 392$. $^\ddagger n = 299$. $^\ddagger n = 385$. eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin.
participants receiving a weekly semaglutide dose of 1.0 mg compared with 0.5 mg.

**Body measurements**

With once-weekly semaglutide, relative bodyweight decreased from baseline to EOS by 4.0–7.3% in the overall populations and 2.7–10.4% in Japanese participants (Figure 3a). Relative changes in bodyweight from baseline to EOS with once-weekly semaglutide were greater versus comparator (placebo or sitagliptin) in all studies in the overall populations and in Japanese participants. These bodyweight changes were greater among participants receiving a weekly semaglutide dose of 1.0 mg compared with 0.5 mg. Similarly, absolute bodyweight reductions were greater among participants receiving a weekly semaglutide dose of 1.0 mg compared with 0.5 mg (Figure 3b). Absolute bodyweight decreased from baseline to EOS with once-weekly semaglutide by 3.67–6.42 kg in the overall populations and 1.85–6.91 kg in Japanese participants. Reductions in BMI with once-weekly semaglutide from baseline to EOS were in the range of 1.3–2.3 kg/m² for the overall populations and 0.7–2.6 kg/m² for Japanese participants (Figure S1). BMI reductions were numerically larger for once-weekly semaglutide than for the comparators and for once-weekly semaglutide 1.0 mg vs 0.5 mg. Changes in BMI were greater in participants who received once-weekly semaglutide 1.0 mg compared with 0.5 mg.

**Composite outcome**

A numerically higher proportion of participants receiving once-weekly semaglutide vs comparators, in both the overall populations and Japanese participants, achieved the composite end-point of HbA\(_1c\) <7% without severe or blood glucose-confirmed symptomatic hypoglycemia and without weight gain by EOS (Figure S2). The proportions of participants receiving once-weekly semaglutide who reached this composite end-point ranged from 54% to 74% in the overall populations and, among Japanese participants, from 63% to 100%. The proportion of participants reaching this composite end-point tended to be higher among participants receiving a weekly semaglutide dose of 1.0 mg compared with 0.5 mg in all trials except SUSTAIN 1, for which the proportions were similar for the two doses of once-weekly semaglutide, for the overall populations, but not in Japanese participants.

**Safety**

No new safety concerns were identified with once-weekly semaglutide in the post-hoc analysis of SUSTAIN 1, 2, 5 and 9 among Japanese participants. AEs in all study participants have been published previously (Table 2). AEs in Japanese participants are summarized in Table 3. There were no AEs leading to death in Japanese participants. More participants receiving semaglutide experienced gastrointestinal AEs, compared with participants...
treated with placebo or sitagliptin, but these rarely led to premature discontinuation of semaglutide (0–13.6% of participants).

The proportion of participants experiencing hypoglycemic episodes was numerically similar or higher among participants receiving once-weekly semaglutide compared with those receiving placebo in SUSTAIN 1, 2 and 9 for both the overall populations and the Japanese participants (Tables 2 and 3). There were no reported severe hypoglycemic episodes in any treatment group among the Japanese participants (Table 3).

DISCUSSION
In the present post-hoc analysis of trial data from the SUSTAIN 1, 2, 5 and 9 studies, participants treated with once-weekly semaglutide experienced clinically relevant reductions in HbA1c in both the overall populations and in the subgroups of Japanese participants in each study. Baseline HbA1c at the start of the studies was similar in the overall populations and Japanese participants. The treatment effect with once-weekly semaglutide on HbA1c was greater in the Japanese cohort across the four studies, with numerically comparable or greater reductions even observed in Japanese participants receiving the lower 0.5 mg dose compared with those receiving the 1.0 mg dose in the overall populations.

More than 60% of participants (overall populations and Japanese participants, who had a baseline HbA1c of 7.0–10.5% at enrollment) achieved the guideline-recommended HbA1c target <7%. A larger proportion of participants treated with once-weekly semaglutide vs comparators achieved that target of HbA1c <7%, and reached the composite end-point of HbA1c <7% without severe or blood glucose-confirmed symptomatic hypoglycemia and without weight gain at EOS. In the overall populations and in Japanese participants, the proportion reaching this composite end-point was higher among participants receiving once-weekly semaglutide 1.0 mg compared with 0.5 mg in all trials except SUSTAIN 1, in which the difference was only observed in Japanese participants. This was likely driven by the proportions of participants achieving the HbA1c target of <7%, which was similar between the two treatment arms in the overall SUSTAIN 1 population (74 and 72% for participants receiving once-weekly semaglutide 0.5 and 1.0 mg, respectively), whereas 100% of participants receiving semaglutide 1.0 mg achieved this target in the Japanese participants, compared with 84% of those receiving semaglutide 0.5 mg. Notably, baseline bodyweight was lower among Japanese participants (69.4–76.7 kg) than in the overall populations (89.5–91.9 kg). However, participants treated with once-weekly semaglutide experienced reductions in bodyweight and BMI in both the overall populations and in the subgroups of Japanese participants in each study, despite this difference at baseline. Due to
the typically lower bodyweight and BMI of Japanese vs Western populations\(^1,5\), these reductions should be monitored carefully by treating physicians.

These findings support those of a previous phase III, open-label trial (\(n = 601\)) of once-weekly semaglutide vs additional oral antidiabetic drugs in Japanese patients with inadequately
Table 2 | Summary of adverse events in the overall population in SUSTAIN 1, 2, 5 and 9

|                  | SUSTAIN 1 | SUSTAIN 2 | SUSTAIN 5 | SUSTAIN 9 |
|------------------|-----------|-----------|-----------|-----------|
|                  | Sema 0.5 mg | Sema 1.0 mg | Sema 0.5 mg | Sema 1.0 mg | Sita 0.5 mg | Sita 1.0 mg | Placebo 0.5 mg | Placebo 1.0 mg |
| n (%)            | (n = 129) | (n = 130) | (n = 409) | (n = 409) | (n = 132) | (n = 131) | (n = 133) | (n = 151) |
| AEs Overall      | 82 (64.1) | 73 (56.2) | 69 (53.5) | 306 (74.8) | 292 (71.4) | 292 (71.7) | 91 (68.9) | 84 (64.1) | 77 (57.9) | 104 (69.3) | 91 (60.3) |
| Japanese         | 9 (47.4)  | 11 (57.9) | 9 (39.1)  | 40 (83.3)  | 35 (81.4)  | 39 (79.6)  | 11 (64.7) | 14 (63.6) | 16 (72.7) | 11 (44.0) | 9 (36.0)  |
| Serious AEs      | 7 (5.5)   | 7 (5.5)   | 5 (3.9)   | 30 (7.3)   | 30 (7.3)   | 29 (7.1)   | 8 (6.1)   | 12 (9.2)  | 9 (6.8)   | 7 (4.7)   | 6 (4.0)   |
| AE related to    |           |           |           |           |           |           |           |           |           |           |           |
| trial product    |           |           |           |           |           |           |           |           |           |           |           |
| Probably         | 21 (16.4) | 31 (23.8) | 8 (6.2)   | 79 (19.3)  | 86 (21.0)  | 35 (8.6)   | 19 (14.4) | 16 (12.2) | 8 (6.0)   | 30 (20.0) | 11 (7.3)  |
| Possibly         | 29 (22.7) | 27 (20.8) | 12 (9.3)  | 109 (26.7) | 120 (29.3) | 56 (13.8)  | 29 (22.0) | 35 (26.7) | 12 (9.0)  | 41 (27.3) | 19 (12.6) |
| AE leading to    | 8 (6.3)   | 7 (5.4)   | 3 (2.3)   | 33 (8.1)   | 39 (9.5)   | 12 (2.9)   | 6 (4.5)   | 8 (6.1)   | 1 (0.8)   | 13 (8.7)  | 3 (2.0)   |
| premature        |           |           |           |           |           |           |           |           |           |           |           |
| treatment        |           |           |           |           |           |           |           |           |           |           |           |
| discontinuation  |           |           |           |           |           |           |           |           |           |           |           |
| GI AEs           | 49 (38.3) | 50 (38.5) | 19 (14.7) | 178 (43.5) | 163 (39.9) | 96 (23.6)  | 36 (27.3) | 45 (34.4) | 21 (15.8) | 56 (37.3) | 20 (13.2) |
| GI AE leading to | 5 (3.9)   | 4 (3.1)   | 1 (0.8)   | 27 (6.6)   | 31 (7.6)   | 3 (0.7)    | 3 (2.3)   | 6 (4.6)   | 0 (0)     | 10 (6.7)  | 0 (0)     |
| premature        |           |           |           |           |           |           |           |           |           |           |           |
| treatment        |           |           |           |           |           |           |           |           |           |           |           |
| discontinuation  |           |           |           |           |           |           |           |           |           |           |           |
| Hypoglycemic     |           |           |           |           |           |           |           |           |           |           |           |
| episodes (ADA    |           |           |           |           |           |           |           |           |           |           |           |
| classified)      |           |           |           |           |           |           |           |           |           |           |           |
| Overall          | 6 (4.7)   | 11 (8.5)  | 7 (5.4)   | 34 (8.3)   | 38 (9.3)   | 46 (11.3)  | 48 (36.4) | 63 (48.1) | 39 (29.3) | 17 (11.3) | 3 (2.0)   |
| Severe           | 0 (0)     | 0 (0)     | 0 (0)     | 0 (0)      | 0 (0)      | 2 (0.5)    | 0 (0)     | 2 (1.5)   | 1 (0.8)   | 1 (0.7)   | 0 (0)     |
| Documented       | 2 (1.6)   | 5 (3.8)   | 2 (1.6)   | 16 (3.9)   | 22 (5.4)   | 20 (4.9)   | 22 (16.7) | 39 (29.8) | 21 (15.8) | 8 (5.3)   | 0 (0)     |
| symptomatic      | 4 (3.1)   | 5 (3.8)   | 2 (1.6)   | 19 (4.6)   | 12 (2.9)   | 15 (3.7)   | 36 (27.3) | 42 (32.1) | 24 (18.0) | 11 (7.3)  | 1 (0.7)   |
| Asymptomatic     | 1 (0.8)   | 1 (0.8)   | 2 (1.6)   | 3 (0.7)    | 5 (1.2)    | 5 (1.2)    | 2 (1.5)   | 6 (4.6)   | 4 (3.0)   | 0 (0)     | 0 (0)     |
| Probably         | 1 (0.8)   | 1 (0.8)   | 3 (2.3)   | 4 (10)     | 6 (1.5)    | 9 (2.2)    | 2 (1.5)   | 7 (5.3)   | 1 (0.8)   | 2 (1.3)   | 2 (1.3)   |
| symptomatic      |           |           |           |           |           |           |           |           |           |           |           |
| Pseudo-hypoglycemia | 1 (0.8) | 1 (0.8) | 3 (2.3) | 4 (10) | 6 (1.5) | 9 (2.2) | 2 (1.5) | 7 (5.3) | 1 (0.8) | 2 (1.3) | 2 (1.3) |

Data are from the ‘on-treatment’ safety analysis set. ADA, American Diabetes Association; AE, adverse event; GI, gastrointestinal; Sema, semaglutide; Sita, sitagliptin.

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Table 3 | Summary of adverse events in Japanese participants in SUSTAIN 1, 2, 5 and 9

| | SUSTAIN 1 | | SUSTAIN 2 | | SUSTAIN 5 | | SUSTAIN 9 |
|---|---|---|---|---|---|---|---|
| | Sema | Sema | Placebo | Sema | Sema | Sita | Sema | Placebo | Sema | Placebo |
| | 0.5 mg (n = 19) | 1.0 mg (n = 19) | (n = 23) | 0.5 mg (n = 48) | 1.0 mg (n = 43) | (n = 49) | 0.5 mg (n = 17) | 1.0 mg (n = 22) | (n = 22) | 1.0 mg (n = 25) |
| AE s | 9 (47.4) | 11 (57.9) | 9 (39.1) | 40 (83.3) | 35 (81.4) | 39 (79.6) | 11 (64.7) | 14 (63.6) | 16 (72.7) | 11 (44.0) | 9 (36.0) |
| Serious AE s | 1 (5.3) | 0 (0) | 0 (0) | 2 (4.2) | 4 (9.3) | 2 (4.1) | 0 (0) | 0 (0) | 1 (4.5) | 0 (0) | 0 (0) |
| AE related to trial product | | | | | | | | | | | |
| Probably | 2 (10.5) | 9 (47.4) | 1 (4.3) | 6 (12.5) | 9 (20.9) | 2 (4.1) | 0 (0) | 4 (18.2) | 0 (0) | 2 (8.0) | 1 (4.0) |
| Possibly | 2 (10.5) | 3 (15.8) | 1 (4.3) | 18 (37.5) | 17 (39.5) | 8 (16.3) | 5 (29.4) | 5 (22.7) | 1 (4.5) | 4 (16.0) | 0 (0) |
| AE leading to premature treatment discontinuation | 0 (0) | 1 (5.3) | 0 (0) | 1 (2.1) | 6 (14.0) | 0 (0) | 2 (11.8) | 3 (13.6) | 0 (0) | 1 (4.0) | 0 (0) |
| GI AE s | 3 (15.8) | 10 (52.6) | 1 (4.3) | 20 (41.7) | 22 (51.2) | 14 (28.6) | 7 (41.2) | 7 (31.8) | 3 (13.6) | 7 (28.0) | 2 (8.0) |
| GI AE leading to premature treatment discontinuation | 0 (0) | 1 (5.3) | 0 (0) | 1 (2.1) | 4 (9.3) | 0 (0) | 2 (11.8) | 3 (13.6) | 0 (0) | 1 (4.0) | 0 (0) |
| Hypoglycemic episodes (ADA classified) | | | | | | | | | | | |
| Overall | 1 (6.3) | 2 (10.5) | 0 (0) | 6 (12.5) | 3 (7.0) | 4 (8.2) | 6 (35.3) | 16 (72.7) | 9 (40.9) | 1 (4.0) | 0 (0) |
| Severe | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Documented symptomatic | 0 (0) | 1 (5.3) | 0 (0) | 3 (6.3) | 2 (4.7) | 1 (2.0) | 2 (11.8) | 8 (36.4) | 2 (9.1) | 1 (4.0) | 0 (0) |
| Asymptomatic | 1 (5.3) | 2 (10.5) | 0 (0) | 4 (8.3) | 1 (2.3) | 1 (2.0) | 6 (35.3) | 11 (50.0) | 7 (31.8) | 0 (0) | 0 (0) |
| Probably symptomatic | 0 (0) | 0 (0) | 0 (0) | 1 (2.1) | 1 (2.3) | 4 (8.2) | 0 (0) | 3 (13.6) | 1 (4.5) | 0 (0) | 0 (0) |
| Pseudo-hypoglycemia | 0 (0) | 0 (0) | 0 (0) | 1 (2.1) | 1 (2.3) | 1 (2.0) | 1 (5.9) | 1 (4.5) | 0 (0) | 0 (0) | 0 (0) |

Data are from the ‘on-treatment’ safety analysis set. ADA, American Diabetes Association; AE, adverse event; GI, gastrointestinal; Sema, semaglutide; Sita, sitagliptin.
controlled type 2 diabetes, in which semaglutide 0.5 and 1.0 mg were associated with significantly greater reductions in HbA1c and bodyweight from baseline vs comparator oral antidiabetic drugs. More than 80% of participants treated with semaglutide achieved the HbA1c target of <7% in the present study. Semaglutide was well tolerated, with no new safety signals identified in this Japanese population (mean age 58.5 years, mean diabetes duration 8.8 years).

The greater treatment effects of semaglutide on HbA1c and bodyweight could be due to differences in the pathophysiology of type 2 diabetes and genetic architecture in East Asian populations compared with those of Western populations. For example, the presence of variants in diabetes-associated loci that are unique to Japanese persons vs Europeans could be linked to differential effects on type 2 diabetes pathways between populations. Furthermore, because bodyweight has an effect on semaglutide exposure, it is possible that Japanese patients experience slightly higher exposure, given their generally lower bodyweight, explaining their greater responses to semaglutide.

A previous post-hoc analysis of the SUSTAIN Japan monotherapy and SUSTAIN Japan oral antidiabetic drug combination trials showed that the reductions in HbA1c and bodyweight achieved with semaglutide are similar across baseline age and BMI subgroups in Japanese participants. It might be advisable to begin treatment with the lower dose of semaglutide, as per the label, in individuals with low BMI, and closely monitor responses before intensifying the dosage based on individual patient needs and characteristics.

In the present post-hoc analysis, once-weekly semaglutide was well tolerated, and no new safety concerns were identified in Japanese participants in SUSTAIN 1, 2, 5 and 9. In each study, the safety profile of once-weekly semaglutide in Japanese participants was comparable with that in the overall population, with a similar incidence of gastrointestinal AEs and documented symptomatic hypoglycemic episodes. As in the overall population, AEs leading to discontinuation in Japanese participants were predominantly gastrointestinal in nature. There were no reported severe hypoglycemic episodes in any treatment group in Japanese patients.

The once-daily oral formulation of semaglutide is also approved for type 2 diabetes treatment in Japan, and the efficacy and safety of oral semaglutide in Japanese patients with type 2 diabetes have been investigated in a post-hoc subgroup analysis of the PIONEER 1, 3, 4 and 8 clinical trials. Similar to the results of our analysis of once-weekly subcutaneous semaglutide, once-daily oral semaglutide 3, 7 or 14 mg was found to be efficacious and well tolerated in Japanese participants. Change from baseline to week 26 in HbA1c was −1.0 to −1.2% points and −1.4 to −1.7%-points for oral semaglutide 7 mg and 14 mg, respectively. Relative changes in bodyweight from baseline to week 26 were 1.0–2.7% and 3.7–4.7% for oral semaglutide 7 mg and 14 mg, respectively.

The main limitation of this exploratory analysis is that it was carried out post-hoc, and although the studies were powered to show statistical significance in the primary outcome in each overall population, they were not powered to analyze the Japanese participants specifically, or to detect any statistically significant differences between overall populations and the Japanese participants. The results should, therefore, be interpreted with caution.

In a post-hoc analysis of the SUSTAIN 1, 2, 5 and 9 studies, participants with type 2 diabetes initiating once-weekly semaglutide experienced improvements from baseline to EOS in HbA1c, bodyweight and BMI, in both the overall populations and Japanese participants. In these studies, >60% of the participants (overall populations and Japanese participants) had an HbA1c <7% at EOS with once-weekly semaglutide at a dose of 0.5 or 1.0 mg. In addition, >60% of the participants treated with once-weekly semaglutide 0.5 or 1.0 mg (overall populations and Japanese participants) reached the composite endpoint of HbA1c <7% without severe or blood glucose-confirmed symptomatic hypoglycemia and without weight gain at EOS. Safety data collected during the studies did not show any new safety concerns with semaglutide among Japanese participants, and support the usefulness of once-weekly semaglutide in this population.

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DISCLOSURE

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JapicCTI-132,366, NCT02305381/JapicCTI-173,542) were approved by either institutional review boards or ethics committees at each site, according to local practice. Informed consent: All patients gave their informed consent. Registry and the registration no. of the study/trial: The trials were first registered on clinicaltrials.gov in February 2014, August 2013, November 2014 and March 2017 (NCT02054897/JapicCTI-142,442, NCT01930188/JapicCTI-132,366, NCT02305381/JapicCTI-142,729, NCT03086330/JapicCTI-173,542), respectively. Animal studies: N/A.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 | Change in body mass index (kg/m²) from baseline to end of study in all and Japanese participants, by treatment group.

Figure S2 | Proportions of patients reaching the composite end-point of glycated hemoglobin <7% without severe or blood glucose-confirmed symptomatic hypoglycemia and without weight gain by end of study for all and Japanese participants, by treatment group.