Supplementary appendix

A phase 1 multiple-ascending dose study of tirzepatide in Japanese participants with type 2 diabetes

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**Supplementary Table 1.** Pharmacokinetic parameters of tirzepatide, week 1 and week 8

|                | 5 mg tirzepatide† | 10 mg tirzepatide‡ | 15 mg tirzepatide§ |
|----------------|-------------------|--------------------|--------------------|
| **Week 1**     |                   |                    |                    |
| N              | 11                | 12                 | 16                 |
| AUC(0-τ) (ng*h/mL) | 48800 (16)       | 26100 (27)         | 54400 (16)         |
| C<sub>max</sub> (ng/mL) | 364 (20)         | 215 (18)           | 442 (23)           |
| t<sub>max</sub> # (h) | 48.00 (23.98, 72.00) | 35.99 (24.00, 72.00) | 48.00 (24.00, 72.00) |
| **Week 8**     |                   |                    |                    |
| N              | 11                | 11<sup>††</sup>    | 12<sup>‡‡</sup>    |
| AUC(0-τ) (ng*h/mL) | 104000 (19)     | 192000 (16)        | 285000 (15)        |
| C<sub>max</sub> (ng/mL) | 838 (22)        | 1520 (15)          | 2270 (17)          |
| t<sub>max</sub> # (h) | 48.00 (23.83, 48.00) | 24.00 (24.00, 48.00) | 48.00 (24.00, 48.05) |
| t<sub>1/2</sub><sup>§§</sup> | 127 (112, 144)  | 135 (105, 186)    | 121 (94.4, 138)    |
| CL/F (L/h)     | 0.0288 (21)      | 0.0311 (25)        | 0.0321 (17)        |
| V<sub>z</sub>/F (L) | 5.27 (15)        | 6.04 (14)          | 5.61 (13)          |
| RA             | 2.12 (14)        | -                  | -                  |
| Peak to trough | 2.14 (12)        | 2.07 (19)          | 1.94 (21)<sup>¶¶</sup> |

Abbreviations: AUC(0-τ), area under the concentration versus time curve during 1 dosing interval; CL/F, apparent total body clearance of drug calculated after extra-vascular administration; C<sub>max</sub>, maximum observed drug concentration; CV, coefficient of variation; RA, accumulation ratio; t<sub>1/2</sub>, half-life associated with the terminal rate constant in noncompartmental analysis; t<sub>max</sub>, time of C<sub>max</sub>; V<sub>z</sub>/F, apparent volume of distribution during the terminal phase after extra-vascular administration (week 8 dose only).

†Participants in the 5 mg treatment group received 5 mg tirzepatide weeks 1–8.
‡Participants in the 10 mg treatment group received 2.5 mg tirzepatide weeks 1–2, followed by 5 mg weeks 3–4, and 10 mg weeks 5–8.
§Participants in the 15 mg treatment group received 5 mg tirzepatide weeks 1–2, followed by 10 mg weeks 3–6, and 15 mg weeks 7–8.
<sup>τ</sup> τ = 168 hours.
<sup>‡</sup> Median (minimum, maximum).
††One participant in the 10 mg tirzepatide group discontinued after receiving 1 dose of tirzepatide (2.5 mg) due to participant decision. Two participants in the 15 mg tirzepatide group did not escalate to 15 mg, per investigator decision.
‡‡One participant in the 15 mg tirzepatide group discontinued after receiving 4 doses of tirzepatide (5, 5, 10, and 10 mg doses) due to an adverse event of decreased appetite. One participant in the 15 mg tirzepatide group skipped dosing on day 43 due to an adverse event not related to study treatment, and did not escalate to 15 mg.
†§Geometric mean (minimum, maximum).
‡¶N = 10.
Supplementary Figure 1. Study design. Dosing was staggered in cohorts 1 and 2 so that an initial group of up to 6 participants receiving tirzepatide and 2 participants receiving placebo were dosed. On days 4 and 32 in cohort 1, and on days 4, 18, and 46 in cohort 2, available safety data were reviewed, and if no relevant safety signals were noted, the remaining participants were dosed. Participants in cohort 3 were dosed after evaluation of safety data of the initial staggered group of cohort 2.
Supplementary Figure 2. Plasma tirzepatide concentration versus double delta heart rate (A and B) or double delta pulse rate (C and D) and day 1 (A and C) and day 50 (B and D). Dashed lines represent 90% confidence intervals. Double delta changes are based on individual participants’ baseline and mean placebo data. Participants in the 5 mg treatment group received 5 mg tirzepatide weeks 1–8. Participants in the 10 mg treatment group received 2.5 mg tirzepatide weeks 1–2, followed by 5 mg weeks 3–4, and 10 mg weeks 5–8. Participants in the 15 mg treatment group received 5 mg tirzepatide weeks 1–2, followed by 10 mg weeks 3–6, and 15 mg weeks 7–8.
Supplementary Figure 2 (continued).
Supplementary Figure 3. Mean pre-dose heart rate (A), pulse rate (B), systolic blood pressure (C), and diastolic blood pressure (D). Participants in the 5 mg treatment group received 5 mg tirzepatide weeks 1–8. Participants in the 10 mg treatment group received 2.5 mg tirzepatide weeks 1–2, followed by 5 mg weeks 3–4, and 10 mg weeks 5–8. Participants in the 15 mg treatment group received 5 mg tirzepatide weeks 1–2, followed by 10 mg weeks 3–6, and 15 mg weeks 7–8.
Supplementary Figure 4. Summary of meal intake. The percentage of meal completed was derived for each patient and then classified into 5 categories (100%, >75% to ≤99%, >50% to ≤75%, >25% to ≤50%, and >0% to ≤25%). The proportion of patients in each category was then determined for each timepoint and displayed by treatment. Participants in the 5 mg treatment group received 5 mg tirzepatide on days 2 and 51. Participants in the 10 mg treatment group received 2.5 mg tirzepatide on day 2 and 10 mg tirzepatide on day 51. Participants in the 15 mg treatment group received 5 mg tirzepatide on day 2 and 15 mg tirzepatide on day 51.
Supplementary Figure 5. Summary of mean of individual data for appetite sensations visual analog score for hunger (A), fullness (B), satiety (C), prospective food consumption (D), and overall appetite (E) scores. Participants in the 5 mg treatment group received 5 mg tirzepatide on days 2 and 51. Participants in the 10 mg treatment group received 2.5 mg on day 2 and 10 mg tirzepatide on day 51. Participants in the 15 mg treatment group received 5 mg tirzepatide on day 2 and 15 mg tirzepatide on day 51. Abbreviations: h, hour; PD, post-dinner; PL, post-lunch; Pre-D, pre-dinner; Pre-L, pre-lunch.
Supplementary Figure 5 (continued).
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