SUPPLEMENTARY APPENDIX

Matching-adjusted indirect comparison method

In sensitivity analysis 4, matching-adjusted indirect comparison (MAIC) method was used to adjust for potential effect modification attributable to baseline HbA1c and body weight.

MAIC is a statistical method that matches patient level data (SURPASS-2) to aggregate data from comparator trials (SUSTAIN FORTE) to reduce bias in treatment comparisons.¹ Treatment effect modifiers that differ between the studies are used to weight the individual patient data to match the characteristics of the comparator’s patient population. For this sensitivity analysis, we matched for baseline HbA1c and body weight due to the differences in the inclusion criteria and imbalance at baseline.

SURPASS-2 patients who had similar HbA1c or body weight to the aggregate data in SUSTAIN-FORTE are weighted higher, similar to a propensity score. Conversely, SURPASS-2 patients who differ in HbA1c and body weight to the aggregate data of SUSTAIN FORTE would have less weight. This matching adjustment ensures both populations are comparable in terms of treatment effect modifiers identified (HbA1c and body weight).

1. Signorovitch JE, Wu EQ, Yu AP, et al. Comparative effectiveness without head-to-head trials: a method for matching-adjusted indirect comparisons applied to psoriasis treatment with adalimumab or etanercept. *Pharmacoeconomics*. 2010;28(10):935–945.
### TABLE S1 Reweighted baseline characteristics in SURPASS-2 following MAIC and baseline characteristics in SUSTAIN FORTE

|                     | Baseline characteristics in SURPASS-2 (TZP 5/10/15 mg + Semaglutide 1mg) | Overall baseline characteristics in SUSTAIN FORTE |
|---------------------|---------------------------------------------------------------------------|--------------------------------------------------|
|                     | TZP 5 mg (original) | TZP 5 mg (post-match) | TZP 10 mg (original) | TZP 10 mg (post-match) | TZP 15 mg (original) | TZP 15 mg (post-match) | N      |
| N                   | 939                | 631                  | 938                 | 641                  | 939                 | 615                  | 961    |
| Age, years          | 56.6 (10.4)        | 55.3 (10.4)          | 57.1 (10.7)         | 55.8 (10.6)          | 56.4 (10.6)         | 55.0 (10.5)          | 58.1 (10.0) |
| Female, n (%)       | 509 (54%)          | 320 (51%)            | 475 (51%)           | 310 (48%)            | 500 (53%)           | 314 (51%)            | 399 (42%) |
| HbA1c, %            | 8.3 (1.1)          | 8.9 (1.2)            | 8.3 (1.0)           | 8.9 (1.1)            | 8.3 (1.0)           | 8.9 (1.1)            | 8.9 (0.6) |
| Diabetes duration, years | 8.7 (6.5)      | 8.7 (6.4)            | 8.3 (5.9)           | 8.4 (5.7)            | 8.5 (6.4)           | 8.3 (6.3)            | 9.5 (6.2) |
| Body weight, kg     | 93.1 (21.4)        | 99.3 (26.3)          | 94.3 (21.9)         | 99.3 (25.0)          | 93.7 (21.5)         | 99.3 (24.6)          | 99.3 (23.5) |
| BMI, kg/m²          | 34 (7)             | 35.5 (8.2)           | 34.2 (6.9)          | 35.5 (7.6)           | 34.3 (7.1)          | 35.7 (7.9)           | 34.6 (7)  |
| SBP, mmHg           | 130 (14)           | 130 (14)             | 131 (13)            | 131 (13)             | 130 (14)            | 130 (14)             | 134 (14) |
| DBP, mmHg           | 79 (9)             | 80 (9)               | 80 (9)              | 79 (9)               | 80 (9)              | 81 (10)              |

Data are mean (SD) or n (%); MAIC uses the approach proposed by Signorovitch et al.,¹ which applies weights on individual patient data in SURPASS-2 based on total baseline characteristics from SUSTAIN FORTE. Baseline HbA1c and body weight were the covariates that were matched for this MAIC. Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; MAIC, matching-adjusted indirect comparison; SBP, systolic blood pressure; SD, standard deviation; TZP, tirzepatide.

¹. Signorovitch JE, Wu EQ, Yu AP, et al. Comparative effectiveness without head-to-head trials: a method for matching-adjusted indirect comparisons applied to psoriasis treatment with adalimumab or etanercept. *Pharmacoeconomics*. 2010;28(10):935–945.
**TABLE S2** Direct comparison of efficacy data reported in SURPASS-2 and SUSTAIN FORTE (efficacy estimand)

| Trial                        | Treatment arm       | HbA1c (%) | Body weight (kg) |
|------------------------------|---------------------|-----------|------------------|
|                              | n       | CFB at week 40 | ETD vs semaglutide 1mg (95% CI) | n       | CFB at week 40 | ETD vs semaglutide 1mg (95% CI) |
| SURPASS-2† (full population) | Tirzepatide 5 mg    | 420       | -2.09 (0.047)    | -0.23 (-0.36, -0.10) | 420       | -7.8 (0.33)    | -1.7 (-2.6, -0.7) |
|                              | Tirzepatide 10 mg   | 405       | -2.37 (0.048)    | -0.51 (-0.64, -0.38) | 402       | -10.3 (0.34)   | -4.1 (-5.0, -3.2) |
|                              | Tirzepatide 15 mg   | 399       | -2.46 (0.048)    | -0.60 (-0.73, -0.47) | 399       | -12.4 (0.34)   | -6.2 (-7.1, -5.3) |
|                              | Semaglutide 1 mg    | 413       | -1.86 (0.048)    | -                    | 414       | -6.2 (0.33)    | -                    |
| SURPASS-2 (refined population on baseline HbA1c 8–10%) | Tirzepatide 5 mg    | 216       | -2.37 (0.07)     | -0.16 (-0.35, 0.03)  | 215       | -7.1 (0.47)    | -1.8 (-3.1, -0.5)  |
|                              | Tirzepatide 10 mg   | 215       | -2.8 (0.07)      | -0.59 (-0.78, -0.40) | 214       | -9.6 (0.46)    | -4.3 (-5.6, -3.0)  |
|                              | Tirzepatide 15 mg   | 209       | -2.84 (0.07)     | -0.63 (-0.82, -0.44) | 208       | -11.6 (0.47)   | -6.3 (-7.6, -5.0)  |
|                              | Semaglutide 1 mg    | 207       | -2.21 (0.07)     | -                    | 207       | -5.3 (0.47)    | -                    |
| SUSTAIN FORTE‡ (full population) | Semaglutide 2 mg    | 433       | -2.2            | -0.23 (-0.36, -0.11) | 434       | -6.9           | -0.93 (-1.68, -0.18) |
|                              | Semaglutide 1 mg    | 422       | -1.9            | -                    | 425       | -6.0           | -                    |
| SUSTAIN FORTE‡ (metformin-only population) | Semaglutide 2 mg    | 207       | -2.3            | -0.23 (-0.41, -0.04) | 209       | -7.7           | -1.15 (-2.24, -0.06) |
|                              | Semaglutide 1 mg    | 198       | -2.1            | -                    | 199       | -6.6           | -                    |

Data are LSM (SE) in SURPASS-2 and estimated means in SUSTAIN FORTE (no SE/SD available in SUSTAIN FORTE); ETD are LSM (95% CI) at week 40. Abbreviations: CFB, change from baseline; CI, confidence interval; ETD, estimated treatment difference; LSM, least-squares mean; SD, standard deviation; SE, standard error.

1. Frias JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. *N Engl J Med*. 2021;385(6):503–515.
2. Frias JP, Auerbach P, Bajaj HS, et al. Efficacy and safety of once-weekly semaglutide 2.0 mg versus 1.0 mg in patients with type 2 diabetes (SUSTAIN FORTE): a double-blind, randomised, phase 3B trial. *Lancet Diabetes Endocrinol*. 2021;9(9):563–574.