

**Supplementary Appendix:** Comparative Efficacy of  
Tirzepatide and Glucagon-Like Peptide-1 Receptor Agonists on  
Cardiovascular Outcomes in Patients with Type 2 Diabetes: A  
Systematic Review and Network Meta-Analysis

## Search Strategy

### MEDLINE:

| #  | Search Strategy                                                              | Results |
|----|------------------------------------------------------------------------------|---------|
| 1  | tirzepatide.mp. or exp Tirzepatide/                                          | 1,318   |
| 2  | GLP-1 receptor agonist.mp. or exp Glucagon-Like Peptide-1 Receptor Agonists/ | 10,207  |
| 3  | albiglutide.mp.                                                              | 265     |
| 4  | dulaglutide.mp.                                                              | 1,079   |
| 5  | efpeglenatide.mp.                                                            | 47      |
| 6  | exenatide.mp. or exp Exenatide/                                              | 4,232   |
| 7  | liraglutide.mp. or exp Liraglutide/                                          | 5,196   |
| 8  | lixisenatide.mp.                                                             | 685     |
| 9  | semaglutide.mp.                                                              | 3,534   |
| 10 | type 2 diabetes.mp. or exp Diabetes Mellitus, Type 2/                        | 264,952 |
| 11 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9                                    | 15,229  |
| 12 | 10 and 11                                                                    | 8,852   |
| 13 | randomized controlled trial.mp. or exp Randomized Controlled Trial/          | 708,224 |
| 14 | 12 and 13                                                                    | 1,213   |
| 15 | limit 14 to (english language and humans)                                    | 1,176   |

Supplemental Table S1. MEDLINE search strategy.

Embase:

| #  | Search Strategy                                                                                                                | Results   |
|----|--------------------------------------------------------------------------------------------------------------------------------|-----------|
| 1  | tirzepatide.mp. or exp tirzepatide/                                                                                            | 3,180     |
| 2  | GLP-1 receptor agonist.mp. or exp glucagon like peptide 1 receptor agonist/                                                    | 67,938    |
| 3  | albiglutide.mp. or exp albiglutide/                                                                                            | 1,804     |
| 4  | dulaglutide.mp. or exp dulaglutide/                                                                                            | 4,482     |
| 5  | efpeglenatide.mp. or exp efpeglenatide/                                                                                        | 275       |
| 6  | exenatide.mp.                                                                                                                  | 5,365     |
| 7  | exp liraglutide/ or liraglutide.mp.                                                                                            | 17,299    |
| 8  | exp lixisenatide/ or lixisenatide.mp.                                                                                          | 3,069     |
| 9  | semaglutide.mp. or exp semaglutide/                                                                                            | 9,943     |
| 10 | type 2 diabetes.mp. or exp non insulin dependent diabetes mellitus/                                                            | 482,658   |
| 11 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9                                                                                      | 68,510    |
| 12 | 10 and 11                                                                                                                      | 36,064    |
| 13 | randomized controlled trial.mp. or exp randomized controlled trial/                                                            | 1,424,267 |
| 14 | 12 and 13                                                                                                                      | 7,027     |
| 15 | limit 14 to (human and english language and "remove clinical trial (clinicaltrials.gov) records" and "remove medline records") | 2,442     |

Supplemental Table S2. Embase search strategy.

**Baseline Table**

| <b>Trial</b>     | <b>Intervention versus Comparator</b> | <b>Title</b>                                                                                                                                                                   | <b>Population</b>                                                                      | <b>Sample Size (N)</b>                 | <b>Age [mean (SD)]</b>                         |
|------------------|---------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|----------------------------------------|------------------------------------------------|
| SURPASS-CVOT     | Tirzepatide vs Dulaglutide            | Comparison of tirzepatide and dulaglutide on major adverse cardiovascular events in participants with type 2 diabetes and atherosclerotic cardiovascular disease: SURPASS-CVOT | T2D with established ASCVD, and BMI $\geq 25$ kg/m <sup>2</sup>                        | Tirzepatide: 6586<br>Dulaglutide: 6579 | Tirzepatide: 64.0<br>Dulaglutide: 64.1         |
| AMPLITUDE-O      | Efpeglenatide vs Placebo              | Cardiovascular and Renal Outcomes with Efpeglenatide in Type 2 Diabetes                                                                                                        | T2D and either a history of CV or kidney disease and at least one other CV risk factor | I: 2717<br>C: 1359                     | I: 64.6 $\pm$ 8.2<br>C: 64.4 $\pm$ 8.3         |
| ELIXA            | Lixisenatide vs Placebo               | Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome                                                                                                      | T2D with MI or hospitalization for unstable angina within past 180 days                | I: 3034<br>C: 3034                     | I: 59.9 $\pm$ 9.7<br>C: 60.6 $\pm$ 9.6         |
| EXSCEL           | Exenatide vs Placebo                  | Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes                                                                                                 | T2D with established CV disease or CV risk factors                                     | I: 7356<br>C: 7396                     | I: 62.0 (range: 56-68)<br>C: 62 (range: 56-68) |
| FLOW             | Semaglutide vs Placebo                | Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes                                                                                              | T2D and CKD                                                                            | I: 1767<br>C: 1766                     | I: 66.6 $\pm$ 9.0<br>C: 66.7 $\pm$ 9.0         |
| Harmony Outcomes | Albiglutide vs Placebo                | Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial    | T2D and established ASCVD                                                              | I: 4731<br>C: 4732                     | I: 64.1 $\pm$ 8.7<br>C: 64.2 $\pm$ 8.7         |

|           |                             |                                                                                                                          |                                                       |                                                     |                                                                        |
|-----------|-----------------------------|--------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|-----------------------------------------------------|------------------------------------------------------------------------|
| LEADER    | Liraglutide vs Placebo      | Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes                                                               | T2D and established CV disease or high CV risk        | I: 4668<br>C: 4672                                  | I: 64.2±7.2<br>C: 64.4±7.2                                             |
| PIONEER 6 | Oral Semaglutide vs Placebo | Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes                                            | T2D and established CV disease or CKD or high CV risk | I: 1591<br>C: 1592                                  | I: 66±7<br>C: 66±7                                                     |
| SOUL      | Oral Semaglutide vs Placebo | Oral Semaglutide and Cardiovascular Outcomes in High-Risk Type 2 Diabetes                                                | T2D with ASCVD, CKD, or both                          | 4,825<br>4,825                                      | I: 66.1±7.6<br>C: 66.1±7.5                                             |
| SUSTAIN 6 | Semaglutide vs Placebo      | Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes                                                 | T2D with established CV disease or high CV risk       | I: male 1013, female 635<br>C: male 989, female 660 | I: male 64.6±7.3, female 64.8±7.1<br>C: male 64.6±7.6, female 64.6±7.5 |
| REWIND    | Dulaglutide vs Placebo      | Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial | T2D with previous CV event or high CV risk            | I: 4949<br>C: 4952                                  | I: 66.2±6.5<br>C: 66.2±6.5                                             |

Supplemental Table S3. Summary of major cardiovascular and renal outcome trials of GLP-1RAs and tirzepatide in patients with T2D and ASCVD or high CV risk. The table outlines the study name, intervention versus (vs) comparator, enrolled population, and sample size (N). I = intervention group; C = control group.

## Risk of Bias

| Study, Year       | Randomization Process | Intervention Deviation | Missing Outcome Data | Measurement of the Outcome | Reporting of the Outcome | Overall Risk |
|-------------------|-----------------------|------------------------|----------------------|----------------------------|--------------------------|--------------|
| AMPLITUDE-O, 2021 | Low Risk              | Low Risk               | Low Risk             | Low Risk                   | Low Risk                 | Low Risk     |
| ELIXA, 2015       | Low Risk              | Low Risk               | Low Risk             | Low Risk                   | Low Risk                 | Low Risk     |
| EXSCEL, 2017      | Low Risk              | Low Risk               | Low Risk             | Low Risk                   | Low Risk                 | Low Risk     |

|                        |          |          |          |          |          |          |
|------------------------|----------|----------|----------|----------|----------|----------|
| FLOW, 2024             | Low Risk | Low Risk | Low Risk | Low Risk | Low Risk | Low Risk |
| Harmony Outcomes, 2018 | Low Risk | Low Risk | Low Risk | Low Risk | Low Risk | Low Risk |
| LEADER, 2016           | Low Risk | Low Risk | Low Risk | Low Risk | Low Risk | Low Risk |
| PIONEER 6, 2019        | Low Risk | Low Risk | Low Risk | Low Risk | Low Risk | Low Risk |
| SOUL, 2025             | Low Risk | Low Risk | Low Risk | Low Risk | Low Risk | Low Risk |
| SUSTAIN 6, 2016        | Low Risk | Low Risk | Low Risk | Low Risk | Low Risk | Low Risk |
| REWIND, 2019           | Low Risk | Low Risk | Low Risk | Low Risk | Low Risk | Low Risk |

Supplemental Table S4. Risk of bias assessment for included randomized controlled trials. The Cochrane Risk of Bias 2 tool was used to assess methodological quality across five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.

### Subgroup Analysis

| MACE                                                             |                   |                   |                   |
|------------------------------------------------------------------|-------------------|-------------------|-------------------|
|                                                                  | Placebo           | Tirzepatide       | GLP-1RA           |
| Placebo                                                          | Placebo           | 1.28 (1.07; 1.52) | 1.17 (1.10; 1.25) |
| Tirzepatide                                                      | 0.78 (0.66; 0.93) | Tirzepatide       |                   |
| GLP-1RA                                                          | 0.85 (0.80; 0.91) |                   | GLP-1RA           |
| Q = 13.9 (p = 0.126), $\tau^2$ = 0.0040, I <sup>2</sup> = 35.26% |                   |                   |                   |

Supplemental Figure S1. Class-level network meta-analysis comparing tirzepatide and the GLP-1RA class to placebo for major adverse cardiovascular events (MACE) restricted to participants with established atherosclerotic cardiovascular disease (ASCVD) or cardiovascular disease (CVD). Hazard ratios (HRs) with 95% confidence intervals represent the row treatment versus the column treatment. Green shading denotes statistically significant benefit, red shading denotes statistically significant relative harm. Values less than 1 favor the active treatment, while values greater than 1 favor the comparator. Measures of between-study heterogeneity (Q statistic,  $\tau^2$ , and I<sup>2</sup>) are reported. This analysis included data from randomized cardiovascular outcomes trials reporting outcomes specifically among participants with established ASCVD, including SURPASS-CVOT, SOUL, LEADER, SUSTAIN-6, PIONEER-6, REWIND, EXSCEL, AMPLITUDE-O, HARMONY Outcomes, and ELIXA. For trials enrolling mixed primary and

secondary prevention populations, hazard ratios derived from prespecified or post-hoc subgroup analyses restricted to participants with established ASCVD or CVD were used. Of note, the trial-defined “established CVD” subgroups in LEADER, SUSTAIN-6, and PIONEER 6 included participants enrolled on the basis of chronic kidney disease alone (i.e., without established ASCVD), in accordance with each study’s predefined subgroup definitions.

| MACE                                                |                   |                   |                   |                   |                   |                   |                   |                   |                   |
|-----------------------------------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| Treatment                                           | Placebo           | Tirzepatide       | Albiglutide       | Dulaglutide       | Efpeglatide       | Exenatide         | Liraglutide       | Lixisenatide      | Semaglutide       |
| Placebo                                             | Placebo           | 1.38 (1.11; 1.70) | 1.28 (1.11; 1.47) | 1.27 (1.05; 1.53) | 1.39 (1.07; 1.81) | 1.11 (1.01; 1.23) | 1.20 (1.07; 1.35) | 0.98 (0.86; 1.12) | 1.17 (1.06; 1.30) |
| Tirzepatide                                         | 0.73 (0.59; 0.90) | Tirzepatide       | 0.93 (0.72; 1.20) | 0.92 (0.83; 1.01) | 1.01 (0.72; 1.41) | 0.81 (0.64; 1.02) | 0.88 (0.69; 1.11) | 0.71 (0.55; 0.92) | 0.85 (0.67; 1.08) |
| Albiglutide                                         | 0.78 (0.68; 0.90) | 1.07 (0.83; 1.38) | Albiglutide       | 0.99 (0.78; 1.25) | 1.08 (0.80; 1.46) | 0.87 (0.73; 1.03) | 0.94 (0.78; 1.13) | 0.76 (0.63; 0.93) | 0.91 (0.77; 1.09) |
| Dulaglutide                                         | 0.79 (0.66; 0.95) | 1.09 (0.99; 1.20) | 1.01 (0.80; 1.28) | Dulaglutide       | 1.10 (0.79; 1.51) | 0.88 (0.71; 1.09) | 0.95 (0.76; 1.19) | 0.77 (0.61; 0.98) | 0.93 (0.75; 1.15) |
| Efpeglatide                                         | 0.72 (0.55; 0.94) | 0.99 (0.71; 1.39) | 0.92 (0.69; 1.24) | 0.91 (0.66; 1.26) | Efpeglatide       | 0.80 (0.60; 1.06) | 0.87 (0.65; 1.16) | 0.71 (0.52; 0.95) | 0.84 (0.64; 1.12) |
| Exenatide                                           | 0.90 (0.81; 0.99) | 1.24 (0.98; 1.56) | 1.15 (0.97; 1.37) | 1.14 (0.92; 1.41) | 1.25 (0.94; 1.66) | Exenatide         | 1.08 (0.93; 1.26) | 0.88 (0.75; 1.04) | 1.06 (0.92; 1.22) |
| Liraglutide                                         | 0.83 (0.74; 0.93) | 1.14 (0.90; 1.45) | 1.06 (0.89; 1.28) | 1.05 (0.84; 1.31) | 1.15 (0.87; 1.54) | 0.92 (0.79; 1.07) | Liraglutide       | 0.81 (0.68; 0.97) | 0.97 (0.84; 1.13) |
| Lixisenatide                                        | 1.02 (0.89; 1.17) | 1.40 (1.09; 1.81) | 1.31 (1.08; 1.59) | 1.29 (1.02; 1.63) | 1.42 (1.05; 1.90) | 1.13 (0.96; 1.34) | 1.23 (1.03; 1.47) | Lixisenatide      | 1.20 (1.01; 1.42) |
| Semaglutide                                         | 0.85 (0.77; 0.94) | 1.17 (0.93; 1.48) | 1.09 (0.92; 1.30) | 1.08 (0.87; 1.34) | 1.18 (0.89; 1.57) | 0.95 (0.82; 1.09) | 1.03 (0.88; 1.20) | 0.84 (0.70; 0.99) | Semaglutide       |
| Q = 2.31 (p = 0.511), $\tau^2$ = 0.0000, $I^2$ = 0% |                   |                   |                   |                   |                   |                   |                   |                   |                   |

Supplemental Figure S2. Agent-level network meta-analysis comparing tirzepatide and the individual GLP-1RA agent to placebo for major adverse cardiovascular events (MACE) restricted to participants with established atherosclerotic cardiovascular disease (ASCVD) or cardiovascular disease (CVD). Hazard ratios (HRs) with 95% confidence intervals represent the row treatment versus the column treatment. Green shading denotes statistically significant benefit, red shading denotes statistically significant relative harm. Values less than 1 favor the active treatment, while values greater than 1 favor the comparator. Measures of between-study heterogeneity (Q statistic,  $\tau^2$ , and  $I^2$ ) are reported. This analysis included data from randomized cardiovascular outcomes trials reporting outcomes specifically among participants with established ASCVD, including SURPASS-CVOT, SOUL, LEADER, SUSTAIN-6, PIONEER-6, REWIND, EXSCel, AMPLITUDE-O, HARMONY Outcomes, and ELIXA. For trials enrolling mixed primary and secondary prevention populations, hazard ratios derived from prespecified or post-hoc subgroup analyses restricted to participants with established ASCVD or CVD were used. Of note, the trial-defined “established CVD” subgroups in LEADER, SUSTAIN-6, and PIONEER 6 included participants enrolled on the basis of chronic kidney disease alone (i.e., without established ASCVD), in accordance with each study’s predefined subgroup definitions.

| A) MACE                                                 |                   |                   |                   | B) CV Mortality                                        |                   |                   |                   |
|---------------------------------------------------------|-------------------|-------------------|-------------------|--------------------------------------------------------|-------------------|-------------------|-------------------|
|                                                         | Placebo           | Tirzepatide       | GLP-1RA           |                                                        | Placebo           | Tirzepatide       | GLP-1RA           |
| Placebo                                                 | Placebo           | 1.28 (1.13; 1.45) | 1.18 (1.11; 1.24) | Placebo                                                | Placebo           | 1.33 (1.13; 1.56) | 1.18 (1.09; 1.28) |
| Tirzepatide                                             | 0.78 (0.69; 0.89) | Tirzepatide       |                   | Tirzepatide                                            | 0.75 (0.64; 0.88) | Tirzepatide       |                   |
| GLP-1RA                                                 | 0.85 (0.80; 0.90) |                   | GLP-1RA           | GLP-1RA                                                | 0.85 (0.78; 0.91) |                   | GLP-1RA           |
| Q = 7.06 (p = 0.315), $\tau^2$ = 0.0008, $I^2$ = 15.05% |                   |                   |                   | Q = 6.04 (p = 0.419), $\tau^2$ = 0.0000, $I^2$ = 0.62% |                   |                   |                   |
| C) All-Cause Mortality                                  |                   |                   |                   | D) Non-Fatal MI                                        |                   |                   |                   |
|                                                         | Placebo           | Tirzepatide       | GLP-1RA           |                                                        | Placebo           | Tirzepatide       | GLP-1RA           |
| Placebo                                                 | Placebo           | 1.37 (1.20; 1.55) | 1.15 (1.08; 1.22) | Placebo                                                | Placebo           | 1.28 (1.07; 1.51) | 1.10 (1.01; 1.19) |
| Tirzepatide                                             | 0.73 (0.64; 0.83) | Tirzepatide       |                   | Tirzepatide                                            | 0.78 (0.66; 0.93) | Tirzepatide       |                   |
| GLP-1RA                                                 | 0.87 (0.82; 0.92) |                   | GLP-1RA           | GLP-1RA                                                | 0.91 (0.84; 0.99) |                   | GLP-1RA           |
| Q = 3.76 (p = 0.709), $\tau^2$ = 0.0000, $I^2$ = 0%     |                   |                   |                   | Q = 3.81 (p = 0.578), $\tau^2$ = 0.0000, $I^2$ = 0%    |                   |                   |                   |
| E) Non-Fatal Stroke                                     |                   |                   |                   |                                                        |                   |                   |                   |
|                                                         | Placebo           | Tirzepatide       | GLP-1RA           |                                                        |                   |                   |                   |
| Placebo                                                 | Placebo           | 1.30 (1.05; 1.60) | 1.18 (1.06; 1.32) |                                                        |                   |                   |                   |
| Tirzepatide                                             | 0.77 (0.62; 0.95) | Tirzepatide       |                   |                                                        |                   |                   |                   |
| GLP-1RA                                                 | 0.85 (0.76; 0.94) |                   | GLP-1RA           |                                                        |                   |                   |                   |
| Q = 6.7 (p = 0.244), $\tau^2$ = 0.0000, $I^2$ = 25.36%  |                   |                   |                   |                                                        |                   |                   |                   |

Supplemental Figure S3. Class-level network meta-analysis comparing tirzepatide, injectable GLP-1RA, and placebo following exclusion of short-acting and oral GLP-1RA trials (ELIXA, PIONEER 6, and SOUL). Outcomes shown include: (A) major adverse cardiovascular events (MACE), (B) cardiovascular (CV) mortality, (C) all-cause mortality, (D) non-fatal myocardial infarction (MI), and (E) non-fatal stroke. Hazard ratios (HRs) with 95% confidence intervals represent the row treatment versus the column treatment. Green shading denotes statistically significant benefit, red shading denotes statistically significant relative harm. Values less than 1 favor the active treatment, while values greater than 1 favor the comparator. Measures of between-study heterogeneity (Q statistic,  $\tau^2$ , and  $I^2$ ) are reported for each outcome.

| A) MACE                                               |                   |                   |                   | B) CV Mortality                                         |                   |                   |                   |
|-------------------------------------------------------|-------------------|-------------------|-------------------|---------------------------------------------------------|-------------------|-------------------|-------------------|
|                                                       | Placebo           | Tirzepatide       | GLP-1RA           |                                                         | Placebo           | Tirzepatide       | GLP-1RA           |
| Placebo                                               | Placebo           | 1.27 (1.14; 1.41) | 1.17 (1.11; 1.22) | Placebo                                                 | Placebo           | 1.29 (1.10; 1.51) | 1.15 (1.07; 1.23) |
| Tirzepatide                                           | 0.79 (0.71; 0.88) | Tirzepatide       |                   | Tirzepatide                                             | 0.78 (0.66; 0.91) | Tirzepatide       |                   |
| GLP-1RA                                               | 0.86 (0.82; 0.90) |                   | GLP-1RA           | GLP-1RA                                                 | 0.87 (0.81; 0.94) |                   | GLP-1RA           |
| Q = 7.09 (p = 0.42), $\tau^2$ = 0.0008, $I^2$ = 1.25% |                   |                   |                   | Q = 7.78 (p = 0.352), $\tau^2$ = 0.0000, $I^2$ = 10.02% |                   |                   |                   |
| C) All-Cause Mortality                                |                   |                   |                   | D) Non-Fatal MI                                         |                   |                   |                   |
|                                                       | Placebo           | Tirzepatide       | GLP-1RA           |                                                         | Placebo           | Tirzepatide       | GLP-1RA           |
| Placebo                                               | Placebo           | 1.35 (1.19; 1.53) | 1.14 (1.07; 1.20) | Placebo                                                 | Placebo           | 1.32 (1.04; 1.66) | 1.13 (1.03; 1.25) |
| Tirzepatide                                           | 0.74 (0.65; 0.84) | Tirzepatide       |                   | Tirzepatide                                             | 0.76 (0.60; 0.96) | Tirzepatide       |                   |
| GLP-1RA                                               | 0.88 (0.83; 0.93) |                   | GLP-1RA           | GLP-1RA                                                 | 0.88 (0.80; 0.98) |                   | GLP-1RA           |
| Q = 7.63 (p = 0.366), $\tau^2$ = 0.0000, $I^2$ = 8.3% |                   |                   |                   | Q = 8.82 (p = 0.184), $\tau^2$ = 0.0056, $I^2$ = 31.94% |                   |                   |                   |
| E) Non-Fatal Stroke                                   |                   |                   |                   |                                                         |                   |                   |                   |
|                                                       | Placebo           | Tirzepatide       | GLP-1RA           |                                                         |                   |                   |                   |
| Placebo                                               | Placebo           | 1.33 (1.08; 1.63) | 1.21 (1.09; 1.34) |                                                         |                   |                   |                   |
| Tirzepatide                                           | 0.75 (0.61; 0.93) | Tirzepatide       |                   |                                                         |                   |                   |                   |
| GLP-1RA                                               | 0.83 (0.75; 0.92) |                   | GLP-1RA           |                                                         |                   |                   |                   |
| Q = 3.04 (p = 0.803), $\tau^2$ = 0.0000, $I^2$ = 0%   |                   |                   |                   |                                                         |                   |                   |                   |

Supplemental Figure S4. Class-level network meta-analysis comparing tirzepatide, GLP-1 receptor agonists (GLP-1RA), and placebo after exclusion of trials with distinct study populations relative to SURPASS-CVOT, specifically ELIXA, which enrolled patients with recent acute coronary syndrome, and FLOW, a dedicated chronic kidney disease outcomes trial. Outcomes shown include: (A) major adverse cardiovascular events (MACE), (B) cardiovascular (CV) mortality, (C) all-cause mortality, (D) non-fatal myocardial infarction (MI), and (E) non-fatal stroke. Hazard ratios (HRs) with 95% confidence intervals represent the row treatment versus the column treatment. Green shading denotes statistically significant benefit, red shading denotes statistically significant relative harm. Values less than 1 favor the active treatment, while

values greater than 1 favor the comparator. Measures of between-study heterogeneity (Q statistic,  $\tau^2$ , and  $I^2$ ) are reported for each outcome.

## Leave One Out Analysis – Class Level Analysis

### Major Adverse Cardiovascular Events

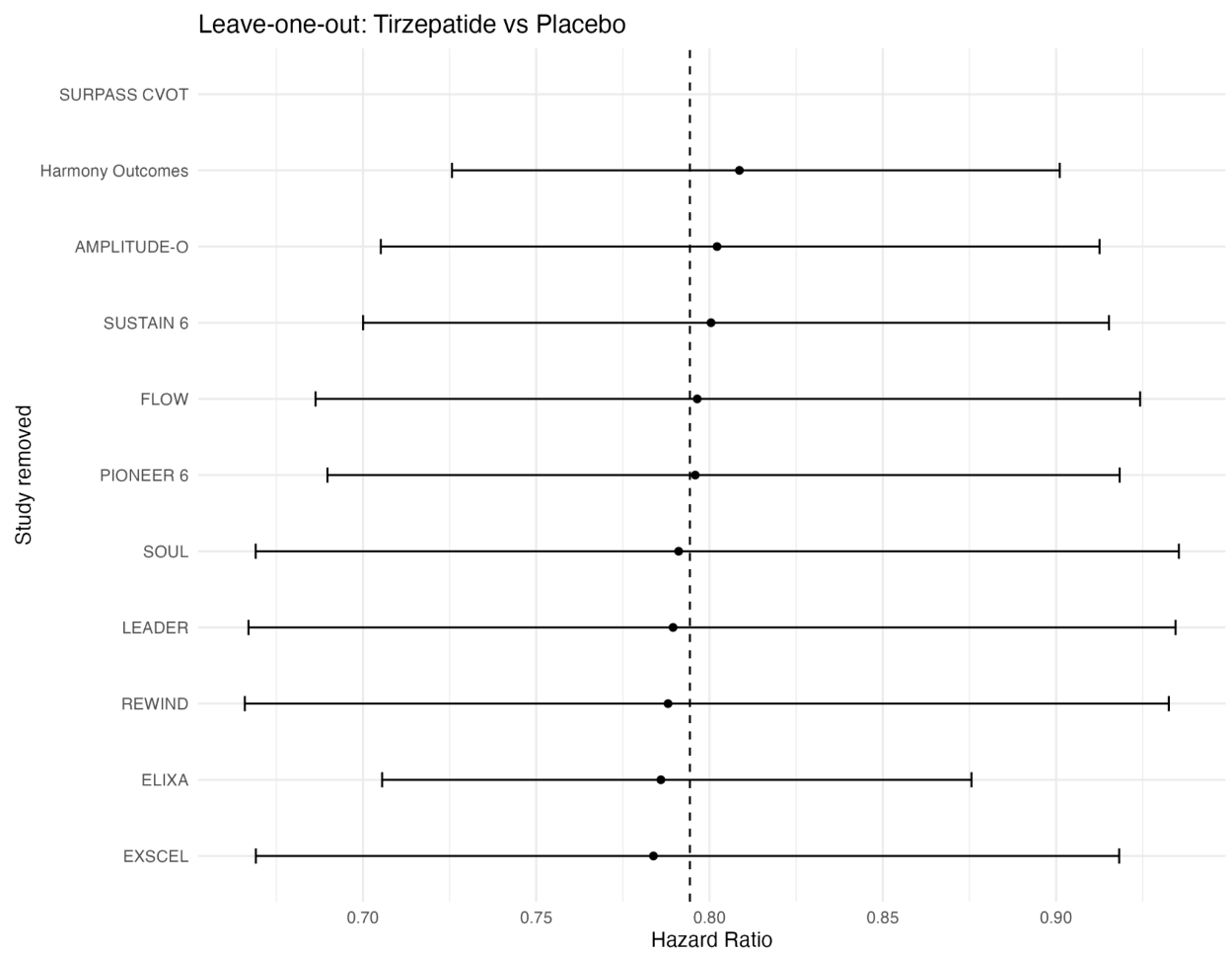
| Study Left Out   | Tau-squared ( $\tau^2$ ) | I-squared ( $I^2$ ) | Cochrane Q | Q p-value |
|------------------|--------------------------|---------------------|------------|-----------|
| AMPLITUDE-O      | 0.001                    | 26.18               | 10.84      | 0.21      |
| ELIXA            | 1.564                    | 0                   | 7.29       | 0.51      |
| EXSCEL           | 0.003                    | 33                  | 11.94      | 0.15      |
| FLOW             | 0.002                    | 37.02               | 12.70      | 0.12      |
| Harmony Outcomes | 0.000                    | 24.42               | 10.58      | 0.23      |
| LEADER           | 0.004                    | 39                  | 13.12      | 0.11      |
| PIONEER 6        | 0.002                    | 37.43               | 12.79      | 0.12      |
| REWIND           | 0.004                    | 38.73               | 13.06      | 0.11      |
| SOUL             | 0.004                    | 38.81               | 13.07      | 0.11      |
| SURPASS CVOT     | 0.002                    | 31.38               | 13.12      | 0.16      |
| SUSTAIN 6        | 0.001                    | 30.01               | 11.43      | 0.18      |

Supplemental Table S5. Leave-one-out sensitivity analysis at the class-level for major adverse cardiovascular events (MACE) showing changes in between-study heterogeneity ( $\tau^2$  and  $I^2$ ) following sequential exclusion of individual trials from the tirzepatide versus placebo comparison.

| Study Left Out   | Comparison             | HR   | Lower 95% CI | Upper 95% CI | Base HR | Delta HR |
|------------------|------------------------|------|--------------|--------------|---------|----------|
| AMPLITUDE-O      | Tirzepatide vs Placebo | 0.80 | 0.71         | 0.91         | 0.79    | 0.008    |
| ELIXA            | Tirzepatide vs Placebo | 0.79 | 0.71         | 0.88         | 0.79    | -0.008   |
| EXSCEL           | Tirzepatide vs Placebo | 0.78 | 0.67         | 0.92         | 0.79    | -0.011   |
| FLOW             | Tirzepatide vs Placebo | 0.80 | 0.69         | 0.92         | 0.79    | 0.002    |
| Harmony Outcomes | Tirzepatide vs Placebo | 0.81 | 0.73         | 0.90         | 0.79    | 0.014    |
| LEADER           | Tirzepatide vs Placebo | 0.79 | 0.67         | 0.93         | 0.79    | -0.005   |
| PIONEER 6        | Tirzepatide vs Placebo | 0.80 | 0.69         | 0.92         | 0.79    | 0.002    |
| REWIND           | Tirzepatide vs Placebo | 0.79 | 0.67         | 0.93         | 0.79    | -0.006   |
| SOUL             | Tirzepatide vs Placebo | 0.79 | 0.67         | 0.94         | 0.79    | -0.003   |

|              |                        |      |      |      |      |       |
|--------------|------------------------|------|------|------|------|-------|
| SURPASS CVOT | Tirzepatide vs Placebo | NA   | NA   | NA   | 0.79 | NA    |
| SUSTAIN 6    | Tirzepatide vs Placebo | 0.80 | 0.70 | 0.92 | 0.79 | 0.006 |

Supplemental Table S6. Leave-one-out sensitivity analysis at the class-level for major adverse cardiovascular events (MACE) comparing tirzepatide versus placebo, presenting hazard ratios with 95% confidence intervals after sequential removal of each individual trial.



Supplemental Figure S5. Leave-one-out sensitivity analysis at the class-level for major adverse cardiovascular events (MACE) comparing tirzepatide versus placebo, demonstrating stable effect estimates across exclusion of individual trials.

Cardiovascular Mortality

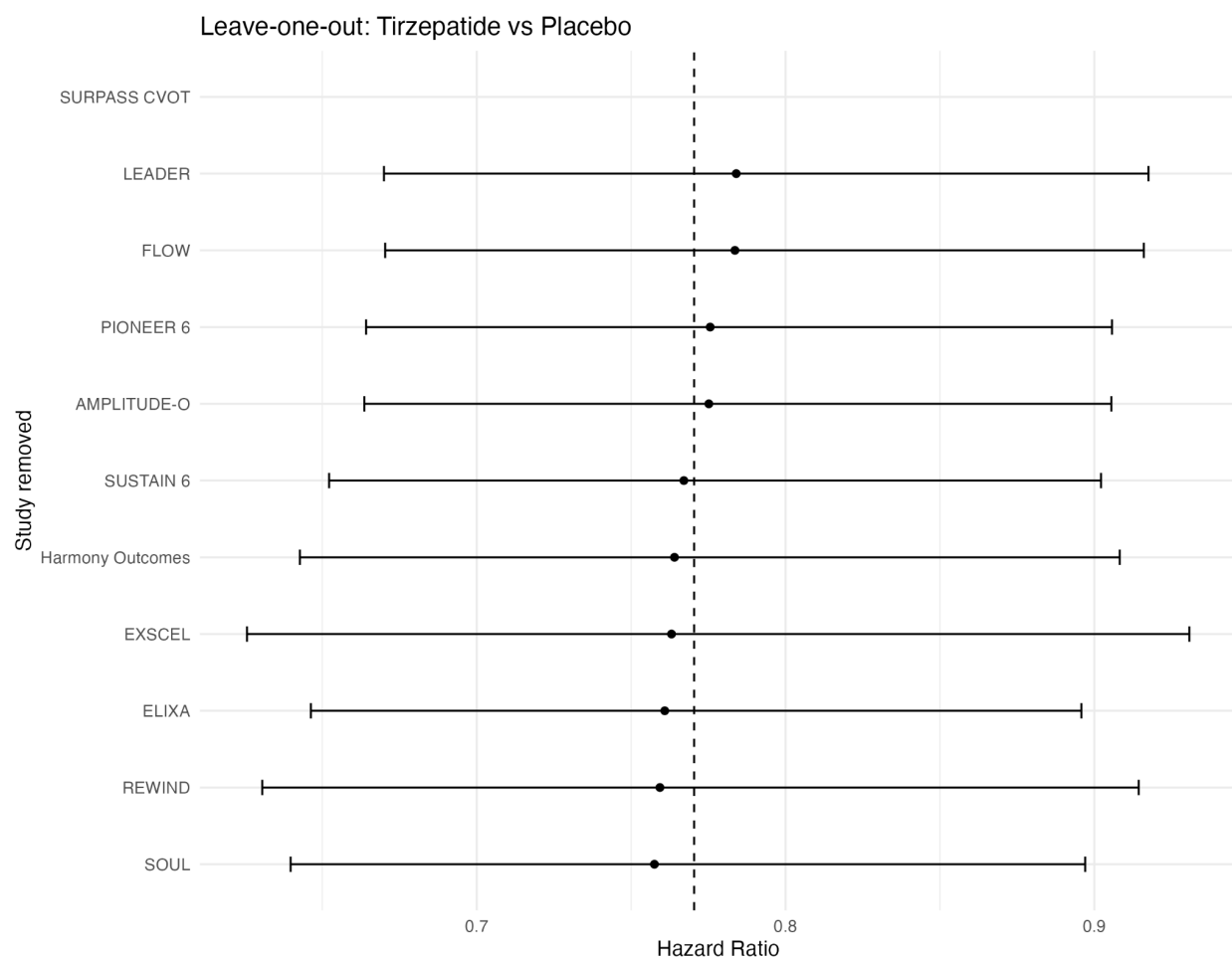
| Study Left Out | Tau-squared ( $\tau^2$ ) | I-squared ( $I^2$ ) | Cochrane Q | Q p-value |
|----------------|--------------------------|---------------------|------------|-----------|
| AMPLITUDE-O    | 0.00                     | 25.46               | 10.73      | 0.22      |

|                  |        |       |       |      |
|------------------|--------|-------|-------|------|
| ELIXA            | 0.001  | 23.97 | 10.52 | 0.23 |
| EXSCEL           | 0.003  | 31.65 | 11.70 | 0.16 |
| FLOW             | 0.000  | 8.17  | 8.71  | 0.37 |
| Harmony Outcomes | 0.001  | 29.87 | 11.41 | 0.18 |
| LEADER           | 0.000  | 20.86 | 10.11 | 0.26 |
| PIONEER 6        | 0.000  | 3.51  | 8.29  | 0.41 |
| REWIND           | 0.002  | 28.99 | 11.27 | 0.19 |
| SOUL             | 0.001  | 25.65 | 10.76 | 0.22 |
| SURPASS CVOT     | 0.000  | 23.50 | 11.76 | 0.23 |
| SUSTAIN 6        | 0.0005 | 29.86 | 11.41 | 0.18 |

Supplemental Table S7. Leave-one-out sensitivity analysis at the class-level for cardiovascular mortality showing changes in between-study heterogeneity ( $\tau^2$  and  $I^2$ ) following sequential exclusion of individual trials from the tirzepatide versus placebo comparison.

| Study Left Out   | Comparison             | HR   | Lower 95% CI | Upper 95% CI | Base HR | Delta HR |
|------------------|------------------------|------|--------------|--------------|---------|----------|
| AMPLITUDE-O      | Tirzepatide vs Placebo | 0.78 | 0.66         | 0.91         | 0.77    | 0.005    |
| ELIXA            | Tirzepatide vs Placebo | 0.76 | 0.65         | 0.90         | 0.77    | -0.009   |
| EXSCEL           | Tirzepatide vs Placebo | 0.76 | 0.63         | 0.93         | 0.77    | -0.007   |
| FLOW             | Tirzepatide vs Placebo | 0.78 | 0.67         | 0.92         | 0.77    | 0.013    |
| Harmony Outcomes | Tirzepatide vs Placebo | 0.76 | 0.64         | 0.91         | 0.77    | -0.006   |
| LEADER           | Tirzepatide vs Placebo | 0.78 | 0.67         | 0.92         | 0.77    | 0.014    |
| PIONEER 6        | Tirzepatide vs Placebo | 0.78 | 0.66         | 0.91         | 0.77    | 0.005    |
| REWIND           | Tirzepatide vs Placebo | 0.76 | 0.63         | 0.91         | 0.77    | -0.011   |
| SOUL             | Tirzepatide vs Placebo | 0.76 | 0.64         | 0.90         | 0.77    | -0.013   |
| SURPASS CVOT     | Tirzepatide vs Placebo | NA   | NA           | NA           | 0.77    | NA       |
| SUSTAIN 6        | Tirzepatide vs Placebo | 0.77 | 0.65         | 0.90         | 0.77    | -0.003   |

Supplemental Table S8. Leave-one-out sensitivity analysis at the class-level for cardiovascular mortality comparing tirzepatide versus placebo, presenting hazard ratios with 95% confidence intervals after sequential removal of each individual trial.



Supplemental Figure S6. Leave-one-out sensitivity analysis at the class-level for cardiovascular mortality comparing tirzepatide versus placebo, demonstrating stable effect estimates across exclusion of individual trials.

### All-Cause Mortality

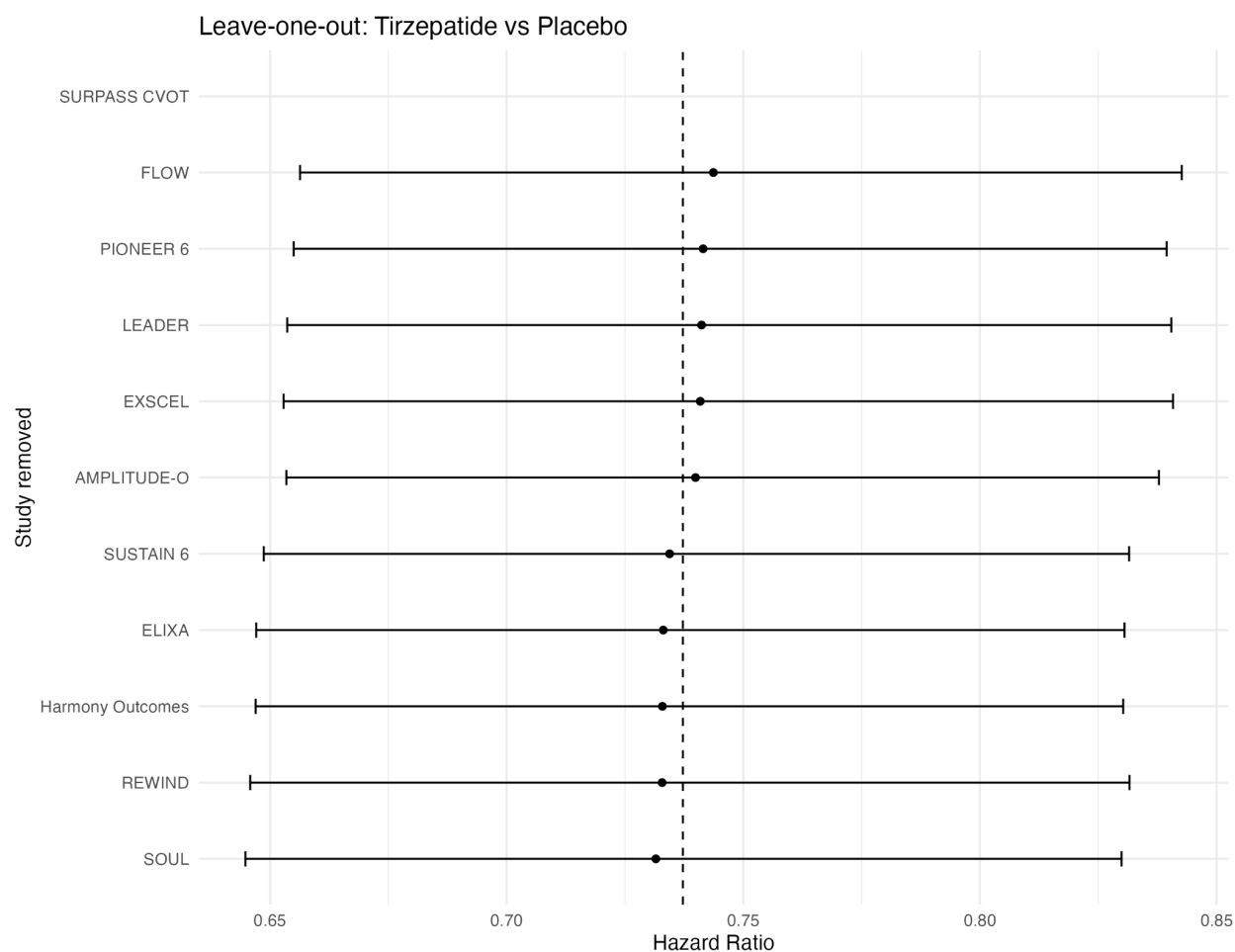
| Study Left Out   | Tau-squared ( $\tau^2$ ) | I-squared ( $I^2$ ) | Cochrane Q | Q p-value |
|------------------|--------------------------|---------------------|------------|-----------|
| AMPLITUDE-O      | 0.000                    | 7.30                | 8.63       | 0.37      |
| ELIXA            | 0.000                    | 7.89                | 8.69       | 0.37      |
| EXSCEL           | 0.000                    | 12.16               | 9.11       | 0.33      |
| FLOW             | 0.000                    | 0.89                | 8.07       | 0.43      |
| Harmony Outcomes | 0.000                    | 6.63                | 8.57       | 0.38      |
| LEADER           | 0.000                    | 11.15               | 9.00       | 0.34      |
| PIONEER 6        | 0.000                    | 0                   | 4.65       | 0.79      |
| REWIND           | 0.000                    | 11.45               | 9.03       | 0.34      |

|                     |       |      |      |      |
|---------------------|-------|------|------|------|
| <b>SOUL</b>         | 0.000 | 9.51 | 8.84 | 0.36 |
| <b>SURPASS CVOT</b> | 0.000 | 2.76 | 9.26 | 0.41 |
| <b>SUSTAIN 6</b>    | 0.000 | 2.97 | 8.24 | 0.41 |

Supplemental Table S9. Leave-one-out sensitivity analysis at the class-level for all-cause mortality showing changes in between-study heterogeneity ( $\tau^2$  and  $I^2$ ) following sequential exclusion of individual trials from the tirzepatide versus placebo comparison.

| Study Left Out          | Comparison             | HR   | Lower 95% CI | Upper 95% CI | Base HR | Delta HR |
|-------------------------|------------------------|------|--------------|--------------|---------|----------|
| <b>AMPLITUDE-O</b>      | Tirzepatide vs Placebo | 0.74 | 0.65         | 0.84         | 0.74    | 0.003    |
| <b>ELIXA</b>            | Tirzepatide vs Placebo | 0.73 | 0.65         | 0.83         | 0.74    | -0.004   |
| <b>EXSCEL</b>           | Tirzepatide vs Placebo | 0.74 | 0.65         | 0.84         | 0.74    | 0.004    |
| <b>FLOW</b>             | Tirzepatide vs Placebo | 0.74 | 0.67         | 0.84         | 0.74    | 0.006    |
| <b>Harmony Outcomes</b> | Tirzepatide vs Placebo | 0.73 | 0.65         | 0.83         | 0.74    | -0.004   |
| <b>LEADER</b>           | Tirzepatide vs Placebo | 0.74 | 0.65         | 0.84         | 0.74    | 0.004    |
| <b>PIONEER 6</b>        | Tirzepatide vs Placebo | 0.74 | 0.66         | 0.84         | 0.74    | 0.004    |
| <b>REWIND</b>           | Tirzepatide vs Placebo | 0.73 | 0.65         | 0.83         | 0.74    | -0.004   |
| <b>SOUL</b>             | Tirzepatide vs Placebo | 0.73 | 0.64         | 0.83         | 0.74    | -0.006   |
| <b>SURPASS CVOT</b>     | Tirzepatide vs Placebo | NA   | NA           | NA           | 0.74    | NA       |
| <b>SUSTAIN 6</b>        | Tirzepatide vs Placebo | 0.73 | 0.65         | 0.83         | 0.74    | -0.003   |

Supplemental Table S10. Leave-one-out sensitivity analysis at the class-level for all-cause mortality events comparing tirzepatide versus placebo, presenting hazard ratios with 95% confidence intervals after sequential removal of each individual trial.



Supplemental Figure S7. Leave-one-out sensitivity analysis at the class-level for all-cause mortality comparing tirzepatide versus placebo, demonstrating stable effect estimates across exclusion of individual trials.

### Non-Fatal Myocardial Infarction

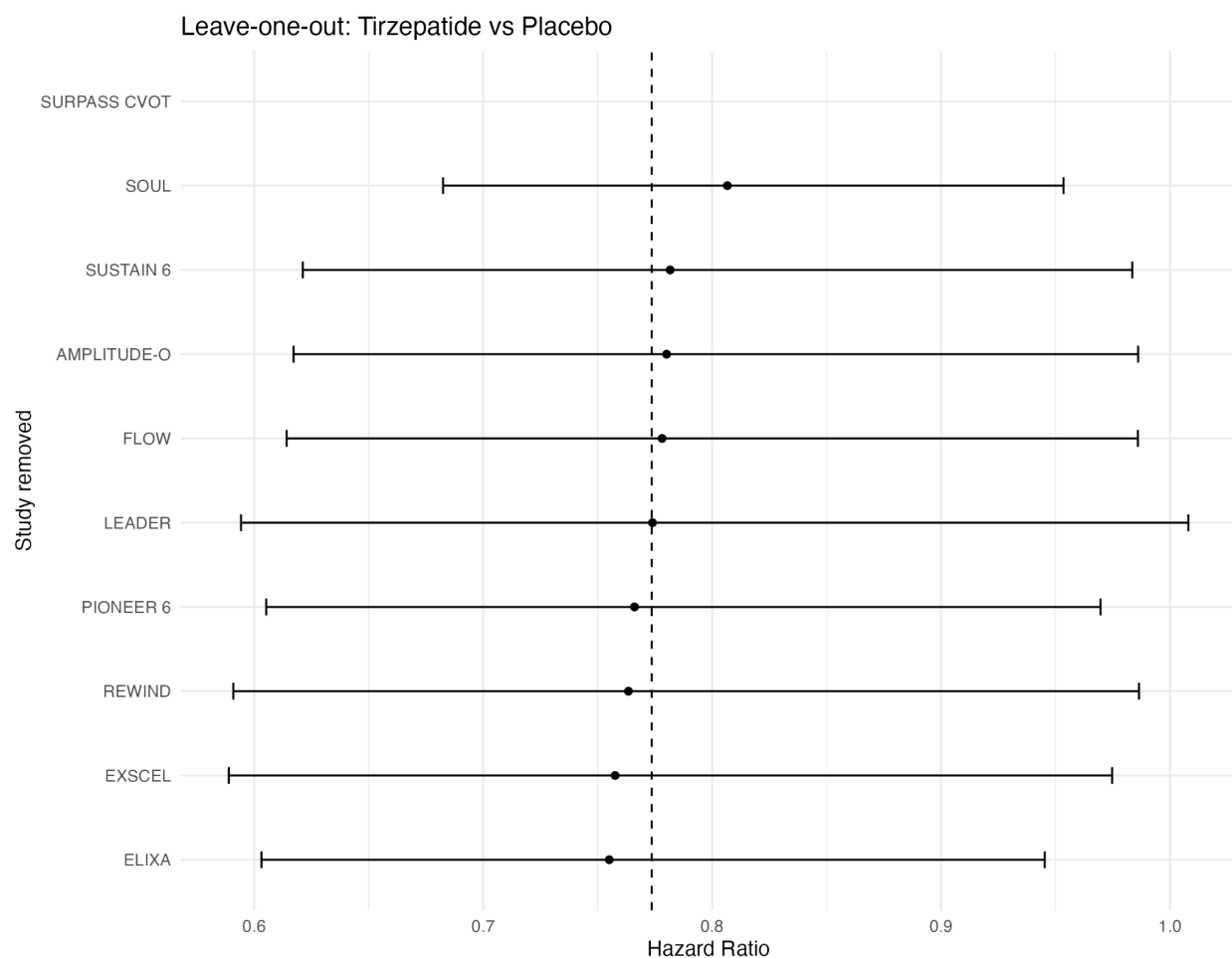
| Study Left Out | Tau-squared ( $\tau^2$ ) | I-squared ( $I^2$ ) | Cochrane Q | Q p-value |
|----------------|--------------------------|---------------------|------------|-----------|
| AMPLITUDE-O    | 0.006                    | 35.32               | 10.82      | 0.15      |
| ELIXA          | 0.005                    | 23.40               | 9.14       | 0.24      |
| EXSCEL         | 0.008                    | 31.99               | 10.29      | 0.17      |
| FLOW           | 0.006                    | 37.08               | 11.13      | 0.13      |
| LEADER         | 0.009                    | 38.61               | 11.40      | 0.12      |
| PIONEER 6      | 0.006                    | 33.01               | 10.45      | 0.16      |
| REWIND         | 0.008                    | 37.86               | 11.26      | 0.13      |
| SOUL           | 0.000                    | 0.00                | 6.34       | 0.50      |

|                     |       |       |       |      |
|---------------------|-------|-------|-------|------|
| <b>SURPASS CVOT</b> | 0.006 | 31.09 | 11.61 | 0.17 |
| <b>SUSTAIN 6</b>    | 0.006 | 32.73 | 10.41 | 0.17 |

Supplemental Table S11. Leave-one-out sensitivity analysis at the class-level for non-fatal myocardial infarction showing changes in between-study heterogeneity ( $\tau^2$  and  $I^2$ ) following sequential exclusion of individual trials from the tirzepatide versus placebo comparison.

| Study Left Out      | Comparison             | HR   | Lower 95% CI | Upper 95% CI | Base HR | Delta HR |
|---------------------|------------------------|------|--------------|--------------|---------|----------|
| <b>AMPLITUDE-O</b>  | Tirzepatide vs Placebo | 0.78 | 0.62         | 0.99         | 0.77    | 0.007    |
| <b>ELIXA</b>        | Tirzepatide vs Placebo | 0.76 | 0.60         | 0.95         | 0.77    | -0.019   |
| <b>EXSCEL</b>       | Tirzepatide vs Placebo | 0.76 | 0.59         | 0.97         | 0.77    | -0.016   |
| <b>FLOW</b>         | Tirzepatide vs Placebo | 0.78 | 0.61         | 0.99         | 0.77    | 0.005    |
| <b>LEADER</b>       | Tirzepatide vs Placebo | 0.77 | 0.59         | 1.01         | 0.77    | 0.00     |
| <b>PIONEER 6</b>    | Tirzepatide vs Placebo | 0.77 | 0.61         | 0.97         | 0.77    | -0.008   |
| <b>REWIND</b>       | Tirzepatide vs Placebo | 0.76 | 0.59         | 0.99         | 0.77    | -0.010   |
| <b>SOUL</b>         | Tirzepatide vs Placebo | 0.81 | 0.68         | 0.95         | 0.77    | 0.033    |
| <b>SURPASS CVOT</b> | Tirzepatide vs Placebo | NA   | NA           | NA           | 0.77    | NA       |
| <b>SUSTAIN 6</b>    | Tirzepatide vs Placebo | 0.78 | 0.62         | 0.98         | 0.77    | 0.008    |

Supplemental Table S12. Leave-one-out sensitivity analysis at the class-level for non-fatal myocardial infarction events comparing tirzepatide versus placebo, presenting hazard ratios with 95% confidence intervals after sequential removal of each individual trial.



Supplemental Figure S8. Leave-one-out sensitivity analysis at the class-level for non-fatal myocardial infarction comparing tirzepatide versus placebo, demonstrating stable effect estimates across exclusion of individual trials.

### Non-Fatal Stroke

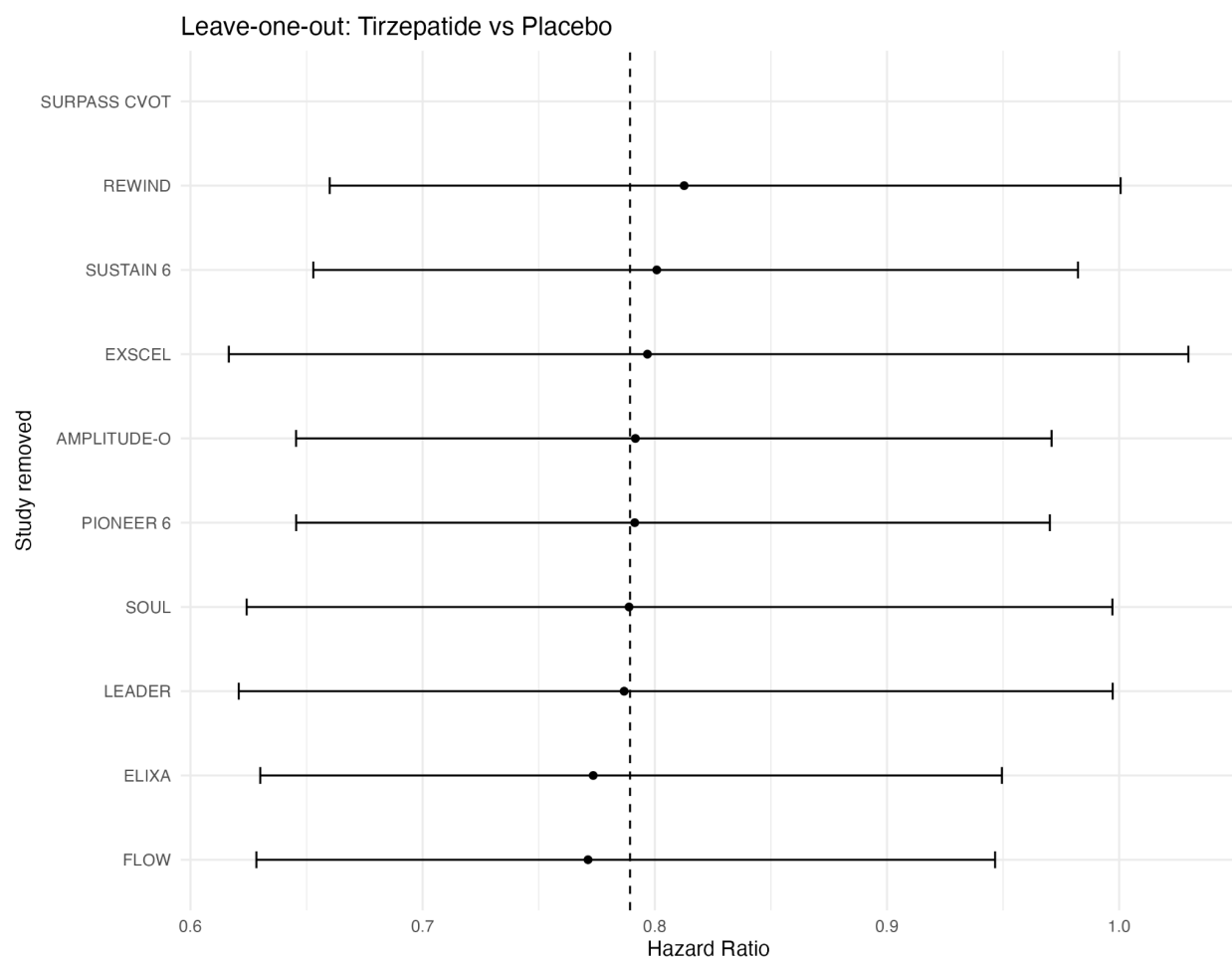
| Study Left Out | Tau-squared ( $\tau^2$ ) | I-squared ( $I^2$ ) | Cochrane Q | Q p-value |
|----------------|--------------------------|---------------------|------------|-----------|
| AMPLITUDE-O    | 0.000                    | 22.89               | 9.08       | 0.25      |
| ELIXA          | 0.000                    | 0.00                | 6.92       | 0.44      |
| EXSCEL         | 0.005                    | 23.28               | 9.12       | 0.24      |
| FLOW           | 0.000                    | 0.00                | 5.74       | 0.57      |
| LEADER         | 0.003                    | 23.18               | 9.11       | 0.24      |
| PIONEER 6      | 0.000                    | 22.26               | 9.00       | 0.25      |
| REWIND         | 0.000                    | 6.80                | 7.51       | 0.38      |
| SOUL           | 0.003                    | 23.59               | 9.16       | 0.24      |

|                     |       |       |      |      |
|---------------------|-------|-------|------|------|
| <b>SURPASS CVOT</b> | 0.000 | 12.85 | 9.18 | 0.33 |
| <b>SUSTAIN 6</b>    | 0.000 | 0.00  | 6.97 | 0.43 |

Supplemental Table S13. Leave-one-out sensitivity analysis at the class-level for non-fatal stroke showing changes in between-study heterogeneity ( $\tau^2$  and  $I^2$ ) following sequential exclusion of individual trials from the tirzepatide versus placebo comparison.

| Study Left Out      | Comparison             | HR   | Lower 95% CI | Upper 95% CI | Base HR | Delta HR |
|---------------------|------------------------|------|--------------|--------------|---------|----------|
| <b>AMPLITUDE-O</b>  | Tirzepatide vs Placebo | 0.79 | 0.65         | 0.97         | 0.79    | 0.002    |
| <b>ELIXA</b>        | Tirzepatide vs Placebo | 0.77 | 0.63         | 0.95         | 0.79    | -0.016   |
| <b>EXSCEL</b>       | Tirzepatide vs Placebo | 0.80 | 0.62         | 1.03         | 0.79    | 0.007    |
| <b>FLOW</b>         | Tirzepatide vs Placebo | 0.77 | 0.63         | 0.95         | 0.79    | -0.018   |
| <b>LEADER</b>       | Tirzepatide vs Placebo | 0.79 | 0.62         | 0.99         | 0.79    | -0.003   |
| <b>PIONEER 6</b>    | Tirzepatide vs Placebo | 0.79 | 0.65         | 0.97         | 0.79    | 0.002    |
| <b>REWIND</b>       | Tirzepatide vs Placebo | 0.81 | 0.66         | 1.00         | 0.79    | 0.023    |
| <b>SOUL</b>         | Tirzepatide vs Placebo | 0.79 | 0.62         | 0.99         | 0.79    | -0.000   |
| <b>SURPASS CVOT</b> | Tirzepatide vs Placebo | NA   | NA           | NA           | 0.79    | NA       |
| <b>SUSTAIN 6</b>    | Tirzepatide vs Placebo | 0.80 | 0.65         | 0.98         | 0.79    | 0.011    |

Supplemental Table S14. Leave-one-out sensitivity analysis at the class-level for non-fatal stroke events comparing tirzepatide versus placebo, presenting hazard ratios with 95% confidence intervals after sequential removal of each individual trial.



Supplemental Figure S9. Leave-one-out sensitivity analysis at the class-level for non-fatal stroke comparing tirzepatide versus placebo, demonstrating stable effect estimates across exclusion of individual trials.

## Leave One Out Analysis – Agent Level Analysis

### Major Adverse Cardiovascular Events

| Study Left Out   | Tau-squared ( $\tau^2$ ) | I-squared ( $I^2$ ) | Cochrane Q | Q p-value |
|------------------|--------------------------|---------------------|------------|-----------|
| AMPLITUDE-O      | 0.000                    | 0.00                | 1.33       | 0.72      |
| ELIXA            | 0.000                    | 0.00                | 1.33       | 0.72      |
| EXSCEL           | 0.000                    | 0.00                | 1.33       | 0.72      |
| FLOW             | 0.000                    | 0.00                | 1.30       | 0.52      |
| Harmony Outcomes | 0.000                    | 0.00                | 1.33       | 0.72      |
| LEADER           | 0.000                    | 0.00                | 1.33       | 0.72      |
| PIONEER 6        | 0.000                    | 0.00                | 1.23       | 0.54      |

|              |       |      |      |      |
|--------------|-------|------|------|------|
| REWIND       | NA    | 0.00 | NA   | NA   |
| SOUL         | 0.000 | 0.00 | 0.43 | 0.81 |
| SURPASS CVOT | 0.000 | 0.00 | 1.33 | 0.72 |
| SUSTAIN 6    | 0.000 | 0.00 | 0.36 | 0.83 |

Supplemental Table S15. Leave-one-out sensitivity analysis at the agent-level for major adverse cardiovascular events (MACE) showing changes in between-study heterogeneity ( $\tau^2$  and  $I^2$ ) following sequential exclusion of individual trials from the tirzepatide versus placebo comparison.

| Study Left Out | Comparison                   | HR   | Lower 95% CI | Upper 95% CI | Base HR | Delta HR |
|----------------|------------------------------|------|--------------|--------------|---------|----------|
| AMPLITUDE-O    | Tirzepatide vs Placebo       | 0.81 | 0.70         | 0.94         | 0.81    | 0.000    |
| AMPLITUDE-O    | Tirzepatide vs Dulaglutide   | 0.92 | 0.83         | 1.01         | 0.92    | 0.000    |
| AMPLITUDE-O    | Tirzepatide vs Albiglutide   | 1.04 | 0.85         | 1.27         | 1.042   | 0.000    |
| AMPLITUDE-O    | Tirzepatide vs Efpeglenatide | NA   | NA           | NA           | 1.11    | NA       |
| AMPLITUDE-O    | Tirzepatide vs Exenatide     | 0.89 | 0.75         | 1.06         | 0.89    | 0.000    |
| AMPLITUDE-O    | Tirzepatide vs Liraglutide   | 0.93 | 0.78         | 1.12         | 0.93    | 0.000    |
| AMPLITUDE-O    | Tirzepatide vs Lixisenatide  | 0.79 | 0.65         | 0.97         | 0.79    | 0.000    |
| AMPLITUDE-O    | Tirzepatide vs Semaglutide   | 0.97 | 0.82         | 1.15         | 0.97    | 0.000    |
| ELIXA          | Tirzepatide vs Placebo       | 0.81 | 0.70         | 0.94         | 0.81    | 0.000    |
| ELIXA          | Tirzepatide vs Dulaglutide   | 0.92 | 0.83         | 1.01         | 0.92    | 0.000    |
| ELIXA          | Tirzepatide vs Albiglutide   | 1.04 | 0.85         | 1.27         | 1.04    | 0.000    |
| ELIXA          | Tirzepatide vs Efpeglenatide | 1.11 | 0.84         | 1.46         | 1.11    | 0.000    |
| ELIXA          | Tirzepatide vs Exenatide     | 0.89 | 0.75         | 1.06         | 0.89    | 0.000    |
| ELIXA          | Tirzepatide vs Liraglutide   | 0.93 | 0.78         | 1.12         | 0.93    | 0.000    |
| ELIXA          | Tirzepatide vs Lixisenatide  | NA   | NA           | NA           | 0.79    | NA       |
| ELIXA          | Tirzepatide vs Semaglutide   | 0.97 | 0.82         | 1.15         | 0.97    | 0.000    |
| EXSCEL         | Tirzepatide vs Placebo       | 0.81 | 0.70         | 0.94         | 0.81    | 0.000    |
| EXSCEL         | Tirzepatide vs Dulaglutide   | 0.92 | 0.83         | 1.01         | 0.92    | 0.000    |
| EXSCEL         | Tirzepatide vs Albiglutide   | 1.04 | 0.85         | 1.27         | 1.04    | 0.000    |

|                         |                              |      |      |      |      |        |
|-------------------------|------------------------------|------|------|------|------|--------|
| <b>EXSCEL</b>           | Tirzepatide vs Efpeglenatide | 1.11 | 0.84 | 1.46 | 1.11 | 0.000  |
| <b>EXSCEL</b>           | Tirzepatide vs Exenatide     | NA   | NA   | NA   | 0.89 | NA     |
| <b>EXSCEL</b>           | Tirzepatide vs Liraglutide   | 0.93 | 0.78 | 1.12 | 0.93 | 0.000  |
| <b>EXSCEL</b>           | Tirzepatide vs Lixisenatide  | 0.79 | 0.65 | 0.97 | 0.79 | 0.000  |
| <b>EXSCEL</b>           | Tirzepatide vs Semaglutide   | 0.97 | 0.82 | 1.15 | 0.97 | 0.000  |
| <b>FLOW</b>             | Tirzepatide vs Placebo       | 0.81 | 0.70 | 0.94 | 0.81 | 0.000  |
| <b>FLOW</b>             | Tirzepatide vs Dulaglutide   | 0.92 | 0.83 | 1.01 | 0.92 | 0.000  |
| <b>FLOW</b>             | Tirzepatide vs Albiglutide   | 1.04 | 0.85 | 1.27 | 1.04 | 0.000  |
| <b>FLOW</b>             | Tirzepatide vs Efpeglenatide | 1.11 | 0.84 | 1.46 | 1.11 | 0.000  |
| <b>FLOW</b>             | Tirzepatide vs Exenatide     | 0.89 | 0.75 | 1.06 | 0.89 | 0.000  |
| <b>FLOW</b>             | Tirzepatide vs Liraglutide   | 0.93 | 0.78 | 1.12 | 0.93 | 0.000  |
| <b>FLOW</b>             | Tirzepatide vs Lixisenatide  | 0.79 | 0.65 | 0.97 | 0.79 | 0.000  |
| <b>FLOW</b>             | Tirzepatide vs Semaglutide   | 0.97 | 0.81 | 1.16 | 0.97 | -0.004 |
| <b>Harmony Outcomes</b> | Tirzepatide vs Placebo       | 0.81 | 0.70 | 0.94 | 0.81 | 0.000  |
| <b>Harmony Outcomes</b> | Tirzepatide vs Dulaglutide   | 0.92 | 0.83 | 1.01 | 0.92 | 0.000  |
| <b>Harmony Outcomes</b> | Tirzepatide vs Albiglutide   | NA   | NA   | NA   | 1.04 | NA     |
| <b>Harmony Outcomes</b> | Tirzepatide vs Efpeglenatide | 1.11 | 0.84 | 1.46 | 1.11 | 0.000  |
| <b>Harmony Outcomes</b> | Tirzepatide vs Exenatide     | 0.89 | 0.75 | 1.06 | 0.89 | 0.000  |
| <b>Harmony Outcomes</b> | Tirzepatide vs Liraglutide   | 0.93 | 0.78 | 1.12 | 0.93 | 0.000  |
| <b>Harmony Outcomes</b> | Tirzepatide vs Lixisenatide  | 0.79 | 0.65 | 0.97 | 0.79 | 0.000  |
| <b>Harmony Outcomes</b> | Tirzepatide vs Semaglutide   | 0.97 | 0.82 | 1.15 | 0.97 | 0.000  |
| <b>LEADER</b>           | Tirzepatide vs Placebo       | 0.81 | 0.70 | 0.94 | 0.81 | 0.000  |
| <b>LEADER</b>           | Tirzepatide vs Dulaglutide   | 0.92 | 0.83 | 1.01 | 0.92 | 0.000  |
| <b>LEADER</b>           | Tirzepatide vs Albiglutide   | 1.04 | 0.85 | 1.27 | 1.04 | 0.000  |
| <b>LEADER</b>           | Tirzepatide vs Efpeglenatide | 1.11 | 0.84 | 1.46 | 1.11 | 0.000  |
| <b>LEADER</b>           | Tirzepatide vs Exenatide     | 0.89 | 0.75 | 1.06 | 0.89 | 0.000  |

|           |                              |      |                   |                   |      |        |
|-----------|------------------------------|------|-------------------|-------------------|------|--------|
| LEADER    | Tirzepatide vs Liraglutide   | NA   | NA                | NA                | 0.93 | NA     |
| LEADER    | Tirzepatide vs Lixisenatide  | 0.79 | 0.65              | 0.97              | 0.79 | 0.000  |
| LEADER    | Tirzepatide vs Semaglutide   | 0.97 | 0.82              | 1.15              | 0.97 | 0.000  |
| PIONEER 6 | Tirzepatide vs Placebo       | 0.81 | 0.70              | 0.94              | 0.81 | 0.000  |
| PIONEER 6 | Tirzepatide vs Dulaglutide   | 0.92 | 0.83              | 1.01              | 0.92 | 0.000  |
| PIONEER 6 | Tirzepatide vs Albiglutide   | 1.04 | 0.85              | 1.27              | 1.04 | 0.000  |
| PIONEER 6 | Tirzepatide vs Efpeglenatide | 1.11 | 0.84              | 1.46              | 1.11 | 0.000  |
| PIONEER 6 | Tirzepatide vs Exenatide     | 0.89 | 0.748349873624205 | 1.05767813076854  | 0.89 | 0.000  |
| PIONEER 6 | Tirzepatide vs Liraglutide   | 0.93 | 0.775729083814131 | 1.11632954581779  | 0.93 | 0.000  |
| PIONEER 6 | Tirzepatide vs Lixisenatide  | 0.79 | 0.649932209437207 | 0.969332100547122 | 0.79 | 0.000  |
| PIONEER 6 | Tirzepatide vs Semaglutide   | 0.97 | 0.8183614759762   | 1.15055015106232  | 0.97 | -0.004 |
| REWIND    | Tirzepatide vs Placebo       | NA   | NA                | NA                | 0.81 | NA     |
| REWIND    | Tirzepatide vs Dulaglutide   | NA   | NA                | NA                | 0.92 | NA     |
| REWIND    | Tirzepatide vs Albiglutide   | NA   | NA                | NA                | 1.04 | NA     |
| REWIND    | Tirzepatide vs Efpeglenatide | NA   | NA                | NA                | 1.11 | NA     |
| REWIND    | Tirzepatide vs Exenatide     | NA   | NA                | NA                | 0.89 | NA     |
| REWIND    | Tirzepatide vs Liraglutide   | NA   | NA                | NA                | 0.93 | NA     |
| REWIND    | Tirzepatide vs Lixisenatide  | NA   | NA                | NA                | 0.79 | NA     |
| REWIND    | Tirzepatide vs Semaglutide   | NA   | NA                | NA                | 0.97 | NA     |
| SOUL      | Tirzepatide vs Placebo       | 0.81 | 0.699797520437937 | 0.936631155237327 | 0.81 | 0.000  |
| SOUL      | Tirzepatide vs Dulaglutide   | 0.92 | 0.834001765078154 | 1.01486595765259  | 0.92 | 0.000  |
| SOUL      | Tirzepatide vs Albiglutide   | 1.04 | 0.847933902826999 | 1.27054424584225  | 1.04 | 0.000  |
| SOUL      | Tirzepatide vs Efpeglenatide | 1.11 | 0.844204073773008 | 1.456960693019    | 1.11 | 0.000  |
| SOUL      | Tirzepatide vs Exenatide     | 0.89 | 0.748349873617016 | 1.0576781307787   | 0.89 | 0.000  |
| SOUL      | Tirzepatide vs Liraglutide   | 0.93 | 0.775729083807045 | 1.11632954582796  | 0.93 | 0.000  |
| SOUL      | Tirzepatide vs Lixisenatide  | 0.79 | 0.649932209431808 | 0.96933210055518  | 0.80 | 0.000  |

|                     |                              |      |                   |                  |      |        |
|---------------------|------------------------------|------|-------------------|------------------|------|--------|
| <b>SOUL</b>         | Tirzepatide vs Semaglutide   | 1.02 | 0.840059194334327 | 1.24830247743021 | 0.97 | 0.050  |
| <b>SURPASS CVOT</b> | Tirzepatide vs Placebo       | NA   | NA                | NA               | 0.81 | NA     |
| <b>SURPASS CVOT</b> | Tirzepatide vs Dulaglutide   | NA   | NA                | NA               | 0.92 | NA     |
| <b>SURPASS CVOT</b> | Tirzepatide vs Albiglutide   | NA   | NA                | NA               | 1.04 | NA     |
| <b>SURPASS CVOT</b> | Tirzepatide vs Efpeglenatide | NA   | NA                | NA               | 1.11 | NA     |
| <b>SURPASS CVOT</b> | Tirzepatide vs Exenatide     | NA   | NA                | NA               | 0.89 | NA     |
| <b>SURPASS CVOT</b> | Tirzepatide vs Liraglutide   | NA   | NA                | NA               | 0.93 | NA     |
| <b>SURPASS CVOT</b> | Tirzepatide vs Lixisenatide  | NA   | NA                | NA               | 0.79 | NA     |
| <b>SURPASS CVOT</b> | Tirzepatide vs Semaglutide   | NA   | NA                | NA               | 0.97 | NA     |
| <b>SUSTAIN 6</b>    | Tirzepatide vs Placebo       | 0.81 | 0.70              | 0.94             | 0.81 | 0.000  |
| <b>SUSTAIN 6</b>    | Tirzepatide vs Dulaglutide   | 0.92 | 0.83              | 1.01             | 0.92 | 0.000  |
| <b>SUSTAIN 6</b>    | Tirzepatide vs Albiglutide   | 1.04 | 0.85              | 1.27             | 1.04 | 0.000  |
| <b>SUSTAIN 6</b>    | Tirzepatide vs Efpeglenatide | 1.11 | 0.84              | 1.46             | 1.11 | 0.000  |
| <b>SUSTAIN 6</b>    | Tirzepatide vs Exenatide     | 0.89 | 0.75              | 1.06             | 0.89 | 0.000  |
| <b>SUSTAIN 6</b>    | Tirzepatide vs Liraglutide   | 0.93 | 0.78              | 1.12             | 0.93 | 0.000  |
| <b>SUSTAIN 6</b>    | Tirzepatide vs Lixisenatide  | 0.79 | 0.65              | 0.97             | 0.79 | 0.000  |
| <b>SUSTAIN 6</b>    | Tirzepatide vs Semaglutide   | 0.96 | 0.81              | 1.14             | 0.97 | -0.015 |

Supplemental Table S16. Leave-one-out sensitivity analysis at the agent-level for major adverse cardiovascular events (MACE) comparing tirzepatide versus placebo, presenting hazard ratios with 95% confidence intervals after sequential removal of each individual trial.

### Cardiovascular Mortality

| Study Left Out | Tau-squared ( $\tau^2$ ) | I-squared ( $I^2$ ) | Cochrane Q | Q p-value |
|----------------|--------------------------|---------------------|------------|-----------|
|----------------|--------------------------|---------------------|------------|-----------|

|                  |       |       |      |      |
|------------------|-------|-------|------|------|
| AMPLITUDE-O      | 0.026 | 58.85 | 7.29 | 0.06 |
| ELIXA            | 0.026 | 58.85 | 7.29 | 0.06 |
| EXSCEL           | 0.026 | 58.85 | 7.29 | 0.06 |
| FLOW             | 0.036 | 52.97 | 4.25 | 0.12 |
| Harmony Outcomes | 0.026 | 58.85 | 7.29 | 0.06 |
| LEADER           | 0.026 | 58.85 | 7.29 | 0.06 |
| PIONEER 6        | 0.015 | 49.85 | 3.99 | 0.14 |
| REWIND           | NA    | NA    | NA   | NA   |
| SOUL             | 0.027 | 46.04 | 3.71 | 0.16 |
| SURPASS CVOT     | 0.026 | 58.85 | 7.29 | 0.06 |
| SUSTAIN 6        | 0.046 | 70.41 | 6.76 | 0.03 |

Supplemental Table S17. Leave-one-out sensitivity analysis at the agent-level for cardiovascular mortality showing changes in between-study heterogeneity ( $\tau^2$  and  $I^2$ ) following sequential exclusion of individual trials from the tirzepatide versus placebo comparison.

| Study Left Out | Comparison                   | HR   | Lower 95% CI | Upper 95% CI | Base HR | Delta HR |
|----------------|------------------------------|------|--------------|--------------|---------|----------|
| AMPLITUDE-O    | Tirzepatide vs Placebo       | 0.81 | 0.50         | 1.32         | 0.81    | 0.000    |
| AMPLITUDE-O    | Tirzepatide vs Dulaglutide   | 0.89 | 0.63         | 1.26         | 0.89    | 0.000    |
| AMPLITUDE-O    | Tirzepatide vs Albiglutide   | 0.87 | 0.46         | 1.64         | 0.87    | 0.000    |
| AMPLITUDE-O    | Tirzepatide vs Efpeglenatide | NA   | NA           | NA           | 1.12    | NA       |
| AMPLITUDE-O    | Tirzepatide vs Exenatide     | 0.92 | 0.50         | 1.68         | 0.92    | 0.000    |
| AMPLITUDE-O    | Tirzepatide vs Liraglutide   | 1.04 | 0.56         | 1.91         | 1.04    | 0.000    |
| AMPLITUDE-O    | Tirzepatide vs Lixisenatide  | 0.83 | 0.44         | 1.55         | 0.83    | 0.000    |
| AMPLITUDE-O    | Tirzepatide vs Semaglutide   | 1.01 | 0.59         | 1.72         | 1.01    | 0.000    |
| ELIXA          | Tirzepatide vs Placebo       | 0.81 | 0.50         | 1.32         | 0.81    | 0.000    |
| ELIXA          | Tirzepatide vs Dulaglutide   | 0.89 | 0.63         | 1.26         | 0.89    | 0.000    |
| ELIXA          | Tirzepatide vs Albiglutide   | 0.87 | 0.46         | 1.64         | 0.87    | 0.000    |
| ELIXA          | Tirzepatide vs Efpeglenatide | 1.12 | 0.57         | 2.24         | 1.12    | 0.000    |

|                         |                              |      |      |      |      |        |
|-------------------------|------------------------------|------|------|------|------|--------|
| <b>ELIXA</b>            | Tirzepatide vs Exenatide     | 0.92 | 0.50 | 1.68 | 0.92 | 0.000  |
| <b>ELIXA</b>            | Tirzepatide vs Liraglutide   | 1.04 | 0.56 | 1.91 | 1.04 | 0.000  |
| <b>ELIXA</b>            | Tirzepatide vs Lixisenatide  | NA   | NA   | NA   | 0.83 | NA     |
| <b>ELIXA</b>            | Tirzepatide vs Semaglutide   | 1.01 | 0.59 | 1.72 | 1.01 | 0.000  |
| <b>EXSCEL</b>           | Tirzepatide vs Placebo       | 0.81 | 0.50 | 1.32 | 0.81 | 0.000  |
| <b>EXSCEL</b>           | Tirzepatide vs Dulaglutide   | 0.89 | 0.63 | 1.26 | 0.89 | 0.000  |
| <b>EXSCEL</b>           | Tirzepatide vs Albiglutide   | 0.87 | 0.46 | 1.64 | 0.87 | 0.000  |
| <b>EXSCEL</b>           | Tirzepatide vs Efpeglenatide | 1.12 | 0.57 | 2.24 | 1.12 | 0.000  |
| <b>EXSCEL</b>           | Tirzepatide vs Exenatide     | NA   | NA   | NA   | 0.92 | NA     |
| <b>EXSCEL</b>           | Tirzepatide vs Liraglutide   | 1.04 | 0.56 | 1.91 | 1.04 | 0.000  |
| <b>EXSCEL</b>           | Tirzepatide vs Lixisenatide  | 0.83 | 0.44 | 1.55 | 0.83 | 0.000  |
| <b>EXSCEL</b>           | Tirzepatide vs Semaglutide   | 1.01 | 0.59 | 1.72 | 1.01 | 0.000  |
| <b>FLOW</b>             | Tirzepatide vs Placebo       | 0.81 | 0.46 | 1.43 | 0.81 | 0.000  |
| <b>FLOW</b>             | Tirzepatide vs Dulaglutide   | 0.89 | 0.60 | 1.33 | 0.89 | 0.000  |
| <b>FLOW</b>             | Tirzepatide vs Albiglutide   | 0.87 | 0.42 | 1.79 | 0.87 | 0.000  |
| <b>FLOW</b>             | Tirzepatide vs Efpeglenatide | 1.12 | 0.52 | 2.43 | 1.12 | 0.000  |
| <b>FLOW</b>             | Tirzepatide vs Exenatide     | 0.92 | 0.46 | 1.84 | 0.92 | 0.000  |
| <b>FLOW</b>             | Tirzepatide vs Liraglutide   | 1.04 | 0.52 | 2.09 | 1.04 | 0.000  |
| <b>FLOW</b>             | Tirzepatide vs Lixisenatide  | 0.83 | 0.40 | 1.69 | 0.83 | 0.000  |
| <b>FLOW</b>             | Tirzepatide vs Semaglutide   | 0.96 | 0.51 | 1.82 | 1.01 | -0.046 |
| <b>Harmony Outcomes</b> | Tirzepatide vs Placebo       | 0.81 | 0.50 | 1.32 | 0.81 | 0.000  |

|                  |                              |      |      |      |      |       |
|------------------|------------------------------|------|------|------|------|-------|
| Harmony Outcomes | Tirzepatide vs Dulaglutide   | 0.89 | 0.63 | 1.26 | 0.89 | 0.000 |
| Harmony Outcomes | Tirzepatide vs Albiglutide   | NA   | NA   | NA   | 0.87 | NA    |
| Harmony Outcomes | Tirzepatide vs Efpeglenatide | 1.12 | 0.57 | 2.24 | 1.12 | 0.000 |
| Harmony Outcomes | Tirzepatide vs Exenatide     | 0.92 | 0.50 | 1.68 | 0.92 | 0.000 |
| Harmony Outcomes | Tirzepatide vs Liraglutide   | 1.04 | 0.56 | 1.91 | 1.04 | 0.000 |
| Harmony Outcomes | Tirzepatide vs Lixisenatide  | 0.83 | 0.44 | 1.55 | 0.83 | 0.000 |
| Harmony Outcomes | Tirzepatide vs Semaglutide   | 1.01 | 0.59 | 1.72 | 1.01 | 0.000 |
| LEADER           | Tirzepatide vs Placebo       | 0.81 | 0.50 | 1.32 | 0.81 | 0.000 |
| LEADER           | Tirzepatide vs Dulaglutide   | 0.89 | 0.63 | 1.26 | 0.89 | 0.000 |
| LEADER           | Tirzepatide vs Albiglutide   | 0.87 | 0.46 | 1.64 | 0.87 | 0.000 |
| LEADER           | Tirzepatide vs Efpeglenatide | 1.12 | 0.57 | 2.24 | 1.12 | 0.000 |
| LEADER           | Tirzepatide vs Exenatide     | 0.92 | 0.50 | 1.68 | 0.92 | 0.000 |
| LEADER           | Tirzepatide vs Liraglutide   | NA   | NA   | NA   | 1.04 | NA    |
| LEADER           | Tirzepatide vs Lixisenatide  | 0.83 | 0.44 | 1.55 | 0.83 | 0.000 |
| LEADER           | Tirzepatide vs Semaglutide   | 1.01 | 0.59 | 1.72 | 1.01 | 0.000 |
| PIONEER 6        | Tirzepatide vs Placebo       | 0.81 | 0.54 | 1.21 | 0.81 | 0.000 |
| PIONEER 6        | Tirzepatide vs Dulaglutide   | 0.89 | 0.67 | 1.18 | 0.89 | 0.000 |
| PIONEER 6        | Tirzepatide vs Albiglutide   | 0.87 | 0.51 | 1.48 | 0.87 | 0.000 |
| PIONEER 6        | Tirzepatide vs Efpeglenatide | 1.12 | 0.62 | 2.04 | 1.12 | 0.000 |
| PIONEER 6        | Tirzepatide vs Exenatide     | 0.92 | 0.56 | 1.51 | 0.92 | 0.000 |
| PIONEER 6        | Tirzepatide vs Liraglutide   | 1.04 | 0.63 | 1.71 | 1.04 | 0.000 |

|                     |                              |      |      |      |      |        |
|---------------------|------------------------------|------|------|------|------|--------|
| <b>PIONEER 6</b>    | Tirzepatide vs Lixisenatide  | 0.83 | 0.49 | 1.39 | 0.83 | 0.000  |
| <b>PIONEER 6</b>    | Tirzepatide vs Semaglutide   | 0.95 | 0.61 | 1.49 | 1.01 | -0.057 |
| <b>REWIND</b>       | Tirzepatide vs Placebo       | NA   | NA   | NA   | 0.81 | NA     |
| <b>REWIND</b>       | Tirzepatide vs Dulaglutide   | NA   | NA   | NA   | 0.89 | NA     |
| <b>REWIND</b>       | Tirzepatide vs Albiglutide   | NA   | NA   | NA   | 0.87 | NA     |
| <b>REWIND</b>       | Tirzepatide vs Efpeglenatide | NA   | NA   | NA   | 1.12 | NA     |
| <b>REWIND</b>       | Tirzepatide vs Exenatide     | NA   | NA   | NA   | 0.92 | NA     |
| <b>REWIND</b>       | Tirzepatide vs Liraglutide   | NA   | NA   | NA   | 1.04 | NA     |
| <b>REWIND</b>       | Tirzepatide vs Lixisenatide  | NA   | NA   | NA   | 0.83 | NA     |
| <b>REWIND</b>       | Tirzepatide vs Semaglutide   | NA   | NA   | NA   | 1.01 | NA     |
| <b>SOUL</b>         | Tirzepatide vs Placebo       | 0.81 | 0.49 | 1.34 | 0.81 | 0.000  |
| <b>SOUL</b>         | Tirzepatide vs Dulaglutide   | 0.89 | 0.63 | 1.27 | 0.89 | 0.000  |
| <b>SOUL</b>         | Tirzepatide vs Albiglutide   | 0.87 | 0.46 | 1.66 | 0.87 | 0.000  |
| <b>SOUL</b>         | Tirzepatide vs Efpeglenatide | 1.12 | 0.56 | 2.26 | 1.12 | 0.000  |
| <b>SOUL</b>         | Tirzepatide vs Exenatide     | 0.92 | 0.50 | 1.70 | 0.92 | 0.000  |
| <b>SOUL</b>         | Tirzepatide vs Liraglutide   | 1.04 | 0.56 | 1.93 | 1.04 | 0.000  |
| <b>SOUL</b>         | Tirzepatide vs Lixisenatide  | 0.83 | 0.44 | 1.57 | 0.83 | 0.000  |
| <b>SOUL</b>         | Tirzepatide vs Semaglutide   | 1.11 | 0.62 | 1.97 | 1.01 | 0.100  |
| <b>SURPASS CVOT</b> | Tirzepatide vs Placebo       | NA   | NA   | NA   | 0.81 | NA     |
| <b>SURPASS CVOT</b> | Tirzepatide vs Dulaglutide   | NA   | NA   | NA   | 0.89 | NA     |
| <b>SURPASS CVOT</b> | Tirzepatide vs Albiglutide   | NA   | NA   | NA   | 0.87 | NA     |

|                     |                              |      |      |      |      |       |
|---------------------|------------------------------|------|------|------|------|-------|
| <b>SURPASS CVOT</b> | Tirzepatide vs Efpeglenatide | NA   | NA   | NA   | 1.12 | NA    |
| <b>SURPASS CVOT</b> | Tirzepatide vs Exenatide     | NA   | NA   | NA   | 0.92 | NA    |
| <b>SURPASS CVOT</b> | Tirzepatide vs Liraglutide   | NA   | NA   | NA   | 1.04 | NA    |
| <b>SURPASS CVOT</b> | Tirzepatide vs Lixisenatide  | NA   | NA   | NA   | 0.83 | NA    |
| <b>SURPASS CVOT</b> | Tirzepatide vs Semaglutide   | NA   | NA   | NA   | 1.01 | NA    |
| <b>SUSTAIN 6</b>    | Tirzepatide vs Placebo       | 0.81 | 0.43 | 1.52 | 0.81 | 0.000 |
| <b>SUSTAIN 6</b>    | Tirzepatide vs Dulaglutide   | 0.89 | 0.57 | 1.38 | 0.89 | 0.000 |
| <b>SUSTAIN 6</b>    | Tirzepatide vs Albiglutide   | 0.87 | 0.39 | 1.93 | 0.87 | 0.000 |
| <b>SUSTAIN 6</b>    | Tirzepatide vs Efpeglenatide | 1.12 | 0.49 | 2.60 | 1.12 | 0.000 |
| <b>SUSTAIN 6</b>    | Tirzepatide vs Exenatide     | 0.92 | 0.43 | 1.99 | 0.92 | 0.000 |
| <b>SUSTAIN 6</b>    | Tirzepatide vs Liraglutide   | 1.04 | 0.48 | 2.25 | 1.04 | 0.000 |
| <b>SUSTAIN 6</b>    | Tirzepatide vs Lixisenatide  | 0.83 | 0.38 | 1.82 | 0.83 | 0.000 |
| <b>SUSTAIN 6</b>    | Tirzepatide vs Semaglutide   | 1.08 | 0.54 | 2.16 | 1.01 | 0.070 |

Supplemental Table S18. Leave-one-out sensitivity analysis at the agent-level for cardiovascular mortality comparing tirzepatide versus placebo, presenting hazard ratios with 95% confidence intervals after sequential removal of each individual trial.

### All-Cause Mortality

| Study Left Out          | Tau-squared ( $\tau^2$ ) | I-squared ( $I^2$ ) | Cochrane Q | Q p-value |
|-------------------------|--------------------------|---------------------|------------|-----------|
| <b>AMPLITUDE-O</b>      | 0.009                    | 56.57               | 6.91       | 0.07      |
| <b>ELIXA</b>            | 0.009                    | 56.57               | 6.91       | 0.07      |
| <b>EXSCEL</b>           | 0.009                    | 56.57               | 6.91       | 0.07      |
| <b>FLOW</b>             | 0.071                    | 65.20               | 5.75       | 0.06      |
| <b>Harmony Outcomes</b> | 0.009                    | 56.57               | 6.91       | 0.07      |
| <b>LEADER</b>           | 0.009                    | 56.57               | 6.91       | 0.07      |
| <b>PIONEER 6</b>        | 0.001                    | 16.19               | 2.39       | 0.30      |

|              |       |       |      |      |
|--------------|-------|-------|------|------|
| REWIND       | NA    | NA    | NA   | NA   |
| SOUL         | 0.062 | 62.96 | 5.40 | 0.07 |
| SURPASS CVOT | 0.009 | 56.57 | 6.91 | 0.07 |
| SUSTAIN 6    | 0.025 | 64.90 | 5.70 | 0.06 |

Supplemental Table S19. Leave-one-out sensitivity analysis at the agent-level for all-cause mortality showing changes in between-study heterogeneity ( $\tau^2$  and  $I^2$ ) following sequential exclusion of individual trials from the tirzepatide versus placebo comparison.

| Study Left Out | Comparison                   | HR    | Lower 95% CI | Upper 95% CI | Base HR | Delta HR |
|----------------|------------------------------|-------|--------------|--------------|---------|----------|
| AMPLITUDE-O    | Tirzepatide vs Placebo       | 0.76  | 0.56         | 1.03         | 0.76    | 0.000    |
| AMPLITUDE-O    | Tirzepatide vs Dulaglutide   | 0.84  | 0.68         | 1.04         | 0.84    | 0.000    |
| AMPLITUDE-O    | Tirzepatide vs Albiglutide   | 0.80  | 0.53         | 1.20         | 0.80    | 0.000    |
| AMPLITUDE-O    | Tirzepatide vs Efpeglenatide | NA    | NA           | NA           | 0.97    | NA       |
| AMPLITUDE-O    | Tirzepatide vs Exenatide     | 0.88  | 0.60         | 1.28         | 0.88    | 0.000    |
| AMPLITUDE-O    | Tirzepatide vs Liraglutide   | 0.89  | 0.61         | 1.31         | 0.89    | 0.000    |
| AMPLITUDE-O    | Tirzepatide vs Lixisenatide  | 0.80  | 0.54         | 1.20         | 0.80    | 0.000    |
| AMPLITUDE-O    | Tirzepatide vs Semaglutide   | 0.89  | 0.63         | 1.25         | 0.89    | 0.000    |
| ELIXA          | Tirzepatide vs Placebo       | 0.76  | 0.56         | 1.03         | 0.76    | 0.000    |
| ELIXA          | Tirzepatide vs Dulaglutide   | 0.84  | 0.68         | 1.04         | 0.84    | 0.000    |
| ELIXA          | Tirzepatide vs Albiglutide   | 0.80  | 0.53         | 1.20         | 0.80    | 0.000    |
| ELIXA          | Tirzepatide vs Efpeglenatide | 0.969 | 0.61         | 1.54         | 0.97    | 0.000    |
| ELIXA          | Tirzepatide vs Exenatide     | 0.879 | 0.60         | 1.28         | 0.88    | 0.000    |
| ELIXA          | Tirzepatide vs Liraglutide   | 0.889 | 0.61         | 1.31         | 0.89    | 0.000    |
| ELIXA          | Tirzepatide vs Lixisenatide  | NA    | NA           | NA           | 0.80    | NA       |

|                  |                              |       |      |      |      |       |
|------------------|------------------------------|-------|------|------|------|-------|
| ELIXA            | Tirzepatide vs Semaglutide   | 0.890 | 0.63 | 1.25 | 0.89 | 0.000 |
| EXSCEL           | Tirzepatide vs Placebo       | 0.756 | 0.56 | 1.03 | 0.76 | 0.000 |
| EXSCEL           | Tirzepatide vs Dulaglutide   | 0.840 | 0.68 | 1.04 | 0.84 | 0.000 |
| EXSCEL           | Tirzepatide vs Albiglutide   | 0.796 | 0.53 | 1.20 | 0.80 | 0.000 |
| EXSCEL           | Tirzepatide vs Efpeglenatide | 0.969 | 0.61 | 1.54 | 0.97 | 0.000 |
| EXSCEL           | Tirzepatide vs Exenatide     | NA    | NA   | NA   | 0.88 | NA    |
| EXSCEL           | Tirzepatide vs Liraglutide   | 0.889 | 0.61 | 1.31 | 0.89 | 0.000 |
| EXSCEL           | Tirzepatide vs Lixisenatide  | 0.804 | 0.54 | 1.20 | 0.80 | 0.000 |
| EXSCEL           | Tirzepatide vs Semaglutide   | 0.890 | 0.63 | 1.25 | 0.89 | 0.000 |
| FLOW             | Tirzepatide vs Placebo       | 0.756 | 0.36 | 1.61 | 0.76 | 0.000 |
| FLOW             | Tirzepatide vs Dulaglutide   | 0.840 | 0.49 | 1.43 | 0.84 | 0.000 |
| FLOW             | Tirzepatide vs Albiglutide   | 0.796 | 0.31 | 2.03 | 0.80 | 0.000 |
| FLOW             | Tirzepatide vs Efpeglenatide | 0.969 | 0.37 | 2.54 | 0.97 | 0.000 |
| FLOW             | Tirzepatide vs Exenatide     | 0.879 | 0.35 | 2.22 | 0.88 | 0.000 |
| FLOW             | Tirzepatide vs Liraglutide   | 0.889 | 0.35 | 2.25 | 0.89 | 0.000 |
| FLOW             | Tirzepatide vs Lixisenatide  | 0.804 | 0.32 | 2.05 | 0.80 | 0.000 |
| FLOW             | Tirzepatide vs Semaglutide   | 0.913 | 0.40 | 2.10 | 0.89 | 0.024 |
| Harmony Outcomes | Tirzepatide vs Placebo       | 0.756 | 0.56 | 1.03 | 0.76 | 0.000 |
| Harmony Outcomes | Tirzepatide vs Dulaglutide   | 0.840 | 0.68 | 1.04 | 0.84 | 0.000 |
| Harmony Outcomes | Tirzepatide vs Albiglutide   | NA    | NA   | NA   | 0.80 | NA    |
| Harmony Outcomes | Tirzepatide vs Efpeglenatide | 0.969 | 0.61 | 1.54 | 0.97 | 0.000 |

|                  |                              |       |      |      |      |        |
|------------------|------------------------------|-------|------|------|------|--------|
| Harmony Outcomes | Tirzepatide vs Exenatide     | 0.879 | 0.60 | 1.28 | 0.88 | 0.000  |
| Harmony Outcomes | Tirzepatide vs Liraglutide   | 0.889 | 0.61 | 1.31 | 0.89 | 0.000  |
| Harmony Outcomes | Tirzepatide vs Lixisenatide  | 0.804 | 0.54 | 1.20 | 0.80 | 0.000  |
| Harmony Outcomes | Tirzepatide vs Semaglutide   | 0.890 | 0.63 | 1.25 | 0.89 | 0.000  |
| LEADER           | Tirzepatide vs Placebo       | 0.756 | 0.56 | 1.03 | 0.76 | 0.000  |
| LEADER           | Tirzepatide vs Dulaglutide   | 0.840 | 0.68 | 1.04 | 0.84 | 0.000  |
| LEADER           | Tirzepatide vs Albiglutide   | 0.796 | 0.53 | 1.20 | 0.80 | 0.000  |
| LEADER           | Tirzepatide vs Efpeglenatide | 0.969 | 0.61 | 1.54 | 0.97 | 0.000  |
| LEADER           | Tirzepatide vs Exenatide     | 0.879 | 0.60 | 1.28 | 0.88 | 0.000  |
| LEADER           | Tirzepatide vs Liraglutide   | NA    | NA   | NA   | 0.89 | NA     |
| LEADER           | Tirzepatide vs Lixisenatide  | 0.804 | 0.54 | 1.20 | 0.80 | 0.000  |
| LEADER           | Tirzepatide vs Semaglutide   | 0.890 | 0.63 | 1.25 | 0.89 | 0.000  |
| PIONEER 6        | Tirzepatide vs Placebo       | 0.756 | 0.63 | 0.91 | 0.76 | 0.000  |
| PIONEER 6        | Tirzepatide vs Dulaglutide   | 0.840 | 0.74 | 0.96 | 0.84 | 0.000  |
| PIONEER 6        | Tirzepatide vs Albiglutide   | 0.796 | 0.60 | 1.05 | 0.80 | 0.000  |
| PIONEER 6        | Tirzepatide vs Efpeglenatide | 0.969 | 0.68 | 1.38 | 0.97 | 0.000  |
| PIONEER 6        | Tirzepatide vs Exenatide     | 0.879 | 0.70 | 1.10 | 0.88 | 0.000  |
| PIONEER 6        | Tirzepatide vs Liraglutide   | 0.889 | 0.70 | 1.13 | 0.89 | 0.000  |
| PIONEER 6        | Tirzepatide vs Lixisenatide  | 0.804 | 0.61 | 1.05 | 0.80 | 0.000  |
| PIONEER 6        | Tirzepatide vs Semaglutide   | 0.855 | 0.69 | 1.06 | 0.89 | -0.035 |
| REWIND           | Tirzepatide vs Placebo       | NA    | NA   | NA   | 0.76 | NA     |

|              |                              |       |      |      |      |       |
|--------------|------------------------------|-------|------|------|------|-------|
| REWIND       | Tirzepatide vs Dulaglutide   | NA    | NA   | NA   | 0.84 | NA    |
| REWIND       | Tirzepatide vs Albiglutide   | NA    | NA   | NA   | 0.80 | NA    |
| REWIND       | Tirzepatide vs Efpeglenatide | NA    | NA   | NA   | 0.97 | NA    |
| REWIND       | Tirzepatide vs Exenatide     | NA    | NA   | NA   | 0.88 | NA    |
| REWIND       | Tirzepatide vs Liraglutide   | NA    | NA   | NA   | 0.89 | NA    |
| REWIND       | Tirzepatide vs Lixisenatide  | NA    | NA   | NA   | 0.80 | NA    |
| REWIND       | Tirzepatide vs Semaglutide   | NA    | NA   | NA   | 0.89 | NA    |
| SOUL         | Tirzepatide vs Placebo       | 0.756 | 0.37 | 1.53 | 0.76 | 0.000 |
| SOUL         | Tirzepatide vs Dulaglutide   | 0.840 | 0.51 | 1.38 | 0.84 | 0.000 |
| SOUL         | Tirzepatide vs Albiglutide   | 0.796 | 0.33 | 1.92 | 0.80 | 0.000 |
| SOUL         | Tirzepatide vs Efpeglenatide | 0.969 | 0.39 | 2.40 | 0.97 | 0.000 |
| SOUL         | Tirzepatide vs Exenatide     | 0.879 | 0.37 | 2.09 | 0.88 | 0.000 |
| SOUL         | Tirzepatide vs Liraglutide   | 0.889 | 0.37 | 2.12 | 0.89 | 0.000 |
| SOUL         | Tirzepatide vs Lixisenatide  | 0.804 | 0.33 | 1.94 | 0.80 | 0.000 |
| SOUL         | Tirzepatide vs Semaglutide   | 0.965 | 0.44 | 2.12 | 0.89 | 0.075 |
| SURPASS CVOT | Tirzepatide vs Placebo       | NA    | NA   | NA   | 0.76 | NA    |
| SURPASS CVOT | Tirzepatide vs Dulaglutide   | NA    | NA   | NA   | 0.84 | NA    |
| SURPASS CVOT | Tirzepatide vs Albiglutide   | NA    | NA   | NA   | 0.80 | NA    |
| SURPASS CVOT | Tirzepatide vs Efpeglenatide | NA    | NA   | NA   | 0.97 | NA    |
| SURPASS CVOT | Tirzepatide vs Exenatide     | NA    | NA   | NA   | 0.88 | NA    |
| SURPASS CVOT | Tirzepatide vs Liraglutide   | NA    | NA   | NA   | 0.89 | NA    |

|                     |                              |       |      |      |      |       |
|---------------------|------------------------------|-------|------|------|------|-------|
| <b>SURPASS CVOT</b> | Tirzepatide vs Lixisenatide  | NA    | NA   | NA   | 0.80 | NA    |
| <b>SURPASS CVOT</b> | Tirzepatide vs Semaglutide   | NA    | NA   | NA   | 0.89 | NA    |
| <b>SUSTAIN 6</b>    | Tirzepatide vs Placebo       | 0.756 | 0.47 | 1.21 | 0.76 | 0.000 |
| <b>SUSTAIN 6</b>    | Tirzepatide vs Dulaglutide   | 0.840 | 0.60 | 1.17 | 0.84 | 0.000 |
| <b>SUSTAIN 6</b>    | Tirzepatide vs Albiglutide   | 0.796 | 0.44 | 1.44 | 0.80 | 0.000 |
| <b>SUSTAIN 6</b>    | Tirzepatide vs Efpeglenatide | 0.969 | 0.51 | 1.83 | 0.97 | 0.000 |
| <b>SUSTAIN 6</b>    | Tirzepatide vs Exenatide     | 0.879 | 0.50 | 1.56 | 0.88 | 0.000 |
| <b>SUSTAIN 6</b>    | Tirzepatide vs Liraglutide   | 0.889 | 0.50 | 1.58 | 0.89 | 0.000 |
| <b>SUSTAIN 6</b>    | Tirzepatide vs Lixisenatide  | 0.804 | 0.45 | 1.45 | 0.80 | 0.000 |
| <b>SUSTAIN 6</b>    | Tirzepatide vs Semaglutide   | 0.952 | 0.57 | 1.60 | 0.89 | 0.062 |

Supplemental Table S20. Leave-one-out sensitivity analysis at the agent-level for all-cause mortality comparing tirzepatide versus placebo, presenting hazard ratios with 95% confidence intervals after sequential removal of each individual trial.

### Non-Fatal Myocardial Infarction

| Study Left Out      | Tau-squared ( $\tau^2$ ) | I-squared ( $I^2$ ) | Cochrane Q | Q p-value |
|---------------------|--------------------------|---------------------|------------|-----------|
| <b>AMPLITUDE-O</b>  | 0.000                    | 8.21                | 3.27       | 0.35      |
| <b>ELIXA</b>        | 0.000                    | 8.21                | 3.27       | 0.35      |
| <b>EXSCEL</b>       | 0.000                    | 8.21                | 3.27       | 0.35      |
| <b>FLOW</b>         | 0.011                    | 38.50               | 3.25       | 0.20      |
| <b>LEADER</b>       | 0.000                    | 8.21                | 3.27       | 0.35      |
| <b>PIONEER 6</b>    | 0.000                    | 0.00                | 0.14       | 0.93      |
| <b>REWIND</b>       | NA                       | NA                  | NA         | NA        |
| <b>SOUL</b>         | 0.001                    | 17.87               | 2.44       | 0.30      |
| <b>SURPASS CVOT</b> | 0.000                    | 8.21                | 3.27       | 0.35      |
| <b>SUSTAIN 6</b>    | 0.013                    | 36.88               | 3.17       | 0.21      |

Supplemental Table S21. Leave-one-out sensitivity analysis at the agent-level for non-fatal myocardial infarction showing changes in between-study heterogeneity ( $\tau^2$  and  $I^2$ ) following sequential exclusion of individual trials from the tirzepatide versus placebo comparison.

| Study Left Out | Comparison                   | HR   | Lower 95% CI | Upper 95% CI | Base HR | Delta HR |
|----------------|------------------------------|------|--------------|--------------|---------|----------|
| AMPLITUDE-O    | Tirzepatide vs Placebo       | 0.83 | 0.65         | 1.05         | 0.83    | 0.000    |
| AMPLITUDE-O    | Tirzepatide vs Dulaglutide   | 0.86 | 0.74         | 1.00         | 0.86    | 0.000    |
| AMPLITUDE-O    | Tirzepatide vs Efpeglenatide | NA   | NA           | NA           | 1.06    | NA       |
| AMPLITUDE-O    | Tirzepatide vs Exenatide     | 0.85 | 0.65         | 1.12         | 0.85    | 0.000    |
| AMPLITUDE-O    | Tirzepatide vs Liraglutide   | 0.94 | 0.70         | 1.26         | 0.94    | 0.000    |
| AMPLITUDE-O    | Tirzepatide vs Lixisenatide  | 0.80 | 0.60         | 1.08         | 0.80    | 0.000    |
| AMPLITUDE-O    | Tirzepatide vs Semaglutide   | 1.06 | 0.79         | 1.40         | 1.06    | 0.000    |
| ELIXA          | Tirzepatide vs Placebo       | 0.83 | 0.65         | 1.05         | 0.83    | 0.000    |
| ELIXA          | Tirzepatide vs Dulaglutide   | 0.86 | 0.74         | 1.00         | 0.86    | 0.000    |
| ELIXA          | Tirzepatide vs Efpeglenatide | 1.06 | 0.69         | 1.62         | 1.06    | 0.000    |
| ELIXA          | Tirzepatide vs Exenatide     | 0.85 | 0.65         | 1.12         | 0.85    | 0.000    |
| ELIXA          | Tirzepatide vs Liraglutide   | 0.94 | 0.70         | 1.26         | 0.94    | 0.000    |
| ELIXA          | Tirzepatide vs Lixisenatide  | NA   | NA           | NA           | 0.80    | NA       |
| ELIXA          | Tirzepatide vs Semaglutide   | 1.06 | 0.79         | 1.40         | 1.06    | 0.000    |
| EXSCEL         | Tirzepatide vs Placebo       | 0.83 | 0.65         | 1.05         | 0.83    | 0.000    |
| EXSCEL         | Tirzepatide vs Dulaglutide   | 0.86 | 0.74         | 1.00         | 0.86    | 0.000    |
| EXSCEL         | Tirzepatide vs Efpeglenatide | 1.06 | 0.69         | 1.62         | 1.06    | 0.000    |
| EXSCEL         | Tirzepatide vs Exenatide     | NA   | NA           | NA           | 0.85    | NA       |
| EXSCEL         | Tirzepatide vs Liraglutide   | 0.94 | 0.70         | 1.26         | 0.94    | 0.000    |
| EXSCEL         | Tirzepatide vs Lixisenatide  | 0.80 | 0.60         | 1.08         | 0.80    | 0.000    |
| EXSCEL         | Tirzepatide vs Semaglutide   | 1.06 | 0.79         | 1.40         | 1.06    | 0.000    |
| FLOW           | Tirzepatide vs Placebo       | 0.83 | 0.57         | 1.20         | 0.83    | 0.000    |
| FLOW           | Tirzepatide vs Dulaglutide   | 0.86 | 0.67         | 1.11         | 0.86    | 0.000    |
| FLOW           | Tirzepatide vs Efpeglenatide | 1.06 | 0.61         | 1.84         | 1.06    | 0.000    |
| FLOW           | Tirzepatide vs Exenatide     | 0.85 | 0.54         | 1.33         | 0.85    | 0.000    |
| FLOW           | Tirzepatide vs Liraglutide   | 0.94 | 0.59         | 1.48         | 0.94    | 0.000    |

|           |                              |      |      |      |      |        |
|-----------|------------------------------|------|------|------|------|--------|
| FLOW      | Tirzepatide vs Lixisenatide  | 0.80 | 0.51 | 1.27 | 0.80 | 0.000  |
| FLOW      | Tirzepatide vs Semaglutide   | 1.03 | 0.67 | 1.59 | 1.06 | -0.023 |
| LEADER    | Tirzepatide vs Placebo       | 0.83 | 0.65 | 1.05 | 0.83 | 0.000  |
| LEADER    | Tirzepatide vs Dulaglutide   | 0.86 | 0.74 | 1.00 | 0.86 | 0.000  |
| LEADER    | Tirzepatide vs Efpeglenatide | 1.06 | 0.69 | 1.62 | 1.06 | 0.000  |
| LEADER    | Tirzepatide vs Exenatide     | 0.85 | 0.65 | 1.12 | 0.85 | 0.000  |
| LEADER    | Tirzepatide vs Liraglutide   | NA   | NA   | NA   | 0.94 | NA     |
| LEADER    | Tirzepatide vs Lixisenatide  | 0.80 | 0.60 | 1.08 | 0.80 | 0.000  |
| LEADER    | Tirzepatide vs Semaglutide   | 1.06 | 0.79 | 1.40 | 1.06 | 0.000  |
| PIONEER 6 | Tirzepatide vs Placebo       | 0.83 | 0.65 | 1.05 | 0.83 | 0.000  |
| PIONEER 6 | Tirzepatide vs Dulaglutide   | 0.86 | 0.74 | 1.00 | 0.86 | 0.000  |
| PIONEER 6 | Tirzepatide vs Efpeglenatide | 1.06 | 0.69 | 1.62 | 1.06 | 0.000  |
| PIONEER 6 | Tirzepatide vs Exenatide     | 0.85 | 0.65 | 1.12 | 0.85 | 0.000  |
| PIONEER 6 | Tirzepatide vs Liraglutide   | 0.94 | 0.70 | 1.26 | 0.94 | 0.000  |
| PIONEER 6 | Tirzepatide vs Lixisenatide  | 0.80 | 0.60 | 1.08 | 0.80 | 0.000  |
| PIONEER 6 | Tirzepatide vs Semaglutide   | 1.10 | 0.83 | 1.47 | 1.06 | 0.046  |
| REWIND    | Tirzepatide vs Placebo       | NA   | NA   | NA   | 0.83 | NA     |
| REWIND    | Tirzepatide vs Dulaglutide   | NA   | NA   | NA   | 0.86 | NA     |
| REWIND    | Tirzepatide vs Efpeglenatide | NA   | NA   | NA   | 1.06 | NA     |
| REWIND    | Tirzepatide vs Exenatide     | NA   | NA   | NA   | 0.85 | NA     |
| REWIND    | Tirzepatide vs Liraglutide   | NA   | NA   | NA   | 0.94 | NA     |
| REWIND    | Tirzepatide vs Lixisenatide  | NA   | NA   | NA   | 0.80 | NA     |
| REWIND    | Tirzepatide vs Semaglutide   | NA   | NA   | NA   | 1.06 | NA     |
| SOUL      | Tirzepatide vs Placebo       | 0.83 | 0.64 | 1.07 | 0.83 | 0.000  |
| SOUL      | Tirzepatide vs Dulaglutide   | 0.86 | 0.73 | 1.01 | 0.86 | 0.000  |
| SOUL      | Tirzepatide vs Efpeglenatide | 1.06 | 0.69 | 1.63 | 1.06 | 0.000  |
| SOUL      | Tirzepatide vs Exenatide     | 0.85 | 0.64 | 1.14 | 0.85 | 0.000  |

|              |                              |      |      |      |      |        |
|--------------|------------------------------|------|------|------|------|--------|
| SOUL         | Tirzepatide vs Liraglutide   | 0.94 | 0.69 | 1.27 | 0.94 | 0.000  |
| SOUL         | Tirzepatide vs Lixisenatide  | 0.80 | 0.59 | 1.09 | 0.80 | 0.000  |
| SOUL         | Tirzepatide vs Semaglutide   | 0.97 | 0.69 | 1.37 | 1.06 | -0.085 |
| SURPASS CVOT | Tirzepatide vs Placebo       | NA   | NA   | NA   | 0.83 | NA     |
| SURPASS CVOT | Tirzepatide vs Dulaglutide   | NA   | NA   | NA   | 0.86 | NA     |
| SURPASS CVOT | Tirzepatide vs Efpeglenatide | NA   | NA   | NA   | 1.06 | NA     |
| SURPASS CVOT | Tirzepatide vs Exenatide     | NA   | NA   | NA   | 0.85 | NA     |
| SURPASS CVOT | Tirzepatide vs Liraglutide   | NA   | NA   | NA   | 0.94 | NA     |
| SURPASS CVOT | Tirzepatide vs Lixisenatide  | NA   | NA   | NA   | 0.80 | NA     |
| SURPASS CVOT | Tirzepatide vs Semaglutide   | NA   | NA   | NA   | 1.06 | NA     |
| SUSTAIN 6    | Tirzepatide vs Placebo       | 0.83 | 0.55 | 1.23 | 0.83 | 0.000  |
| SUSTAIN 6    | Tirzepatide vs Dulaglutide   | 0.86 | 0.66 | 1.13 | 0.86 | 0.000  |
| SUSTAIN 6    | Tirzepatide vs Efpeglenatide | 1.06 | 0.60 | 1.88 | 1.06 | 0.000  |
| SUSTAIN 6    | Tirzepatide vs Exenatide     | 0.85 | 0.53 | 1.37 | 0.85 | 0.000  |
| SUSTAIN 6    | Tirzepatide vs Liraglutide   | 0.94 | 0.58 | 1.53 | 0.94 | 0.000  |
| SUSTAIN 6    | Tirzepatide vs Lixisenatide  | 0.80 | 0.49 | 1.31 | 0.80 | 0.000  |
| SUSTAIN 6    | Tirzepatide vs Semaglutide   | 1.01 | 0.64 | 1.59 | 1.06 | -0.047 |

Supplemental Table S22. Leave-one-out sensitivity analysis at the agent-level for non-fatal myocardial infarction comparing tirzepatide versus placebo, presenting hazard ratios with 95% confidence intervals after sequential removal of each individual trial.

#### Non-Fatal Stroke

| Study Left Out | Tau-squared ( $\tau^2$ ) | I-squared ( $I^2$ ) | Cochrane Q | Q p-value |
|----------------|--------------------------|---------------------|------------|-----------|
| AMPLITUDE-O    | 0.040                    | 44.81               | 5.44       | 0.14      |
| ELIXA          | 0.040                    | 44.81               | 5.44       | 0.14      |
| EXSCEL         | 0.040                    | 44.81               | 5.44       | 0.14      |
| FLOW           | 0.013                    | 0.00                | 1.93       | 0.38      |
| LEADER         | 0.040                    | 44.81               | 5.44       | 0.14      |
| PIONEER 6      | 0.059                    | 61.44               | 5.19       | 0.07      |

|              |       |       |      |      |
|--------------|-------|-------|------|------|
| REWIND       | NA    | NA    | NA   | NA   |
| SOUL         | 0.103 | 63.02 | 5.41 | 0.07 |
| SURPASS CVOT | 0.040 | 44.81 | 5.44 | 0.14 |
| SUSTAIN 6    | 0.015 | 22.45 | 2.58 | 0.28 |

Supplemental Table S23. Leave-one-out sensitivity analysis at the agent-level for non-fatal stroke showing changes in between-study heterogeneity ( $\tau^2$  and  $I^2$ ) following sequential exclusion of individual trials from the tirzepatide versus placebo comparison.

| Study Left Out | Comparison                   | HR    | Lower 95% CI | Upper 95% CI | Base HR | Delta HR |
|----------------|------------------------------|-------|--------------|--------------|---------|----------|
| AMPLITUDE-O    | Tirzepatide vs Placebo       | 0.69  | 0.37         | 1.29         | 0.69    | 0.000    |
| AMPLITUDE-O    | Tirzepatide vs Dulaglutide   | 0.91  | 0.59         | 1.40         | 0.91    | 0.000    |
| AMPLITUDE-O    | Tirzepatide vs Efpeglenatide | NA    | NA           | NA           | 0.86    | NA       |
| AMPLITUDE-O    | Tirzepatide vs Exenatide     | 0.81  | 0.38         | 1.74         | 0.81    | 0.000    |
| AMPLITUDE-O    | Tirzepatide vs Liraglutide   | 0.78  | 0.36         | 1.67         | 0.78    | 0.000    |
| AMPLITUDE-O    | Tirzepatide vs Lixisenatide  | 0.62  | 0.27         | 1.39         | 0.62    | 0.000    |
| AMPLITUDE-O    | Tirzepatide vs Semaglutide   | 0.79  | 0.40         | 1.57         | 0.79    | 0.000    |
| ELIXA          | Tirzepatide vs Placebo       | 0.69  | 0.37         | 1.29         | 0.69    | 0.000    |
| ELIXA          | Tirzepatide vs Dulaglutide   | 0.91  | 0.59         | 1.40         | 0.91    | 0.000    |
| ELIXA          | Tirzepatide vs Efpeglenatide | 0.86  | 0.35         | 2.11         | 0.86    | 0.000    |
| ELIXA          | Tirzepatide vs Exenatide     | 0.814 | 0.38         | 1.74         | 0.81    | 0.000    |
| ELIXA          | Tirzepatide vs Liraglutide   | 0.777 | 0.36         | 1.67         | 0.78    | 0.000    |
| ELIXA          | Tirzepatide vs Lixisenatide  | NA    | NA           | NA           | 0.62    | NA       |
| ELIXA          | Tirzepatide vs Semaglutide   | 0.792 | 0.40         | 1.57         | 0.79    | 0.000    |
| EXSCEL         | Tirzepatide vs Placebo       | 0.692 | 0.37         | 1.29         | 0.69    | 0.000    |
| EXSCEL         | Tirzepatide vs Dulaglutide   | 0.910 | 0.59         | 1.40         | 0.91    | 0.000    |
| EXSCEL         | Tirzepatide vs Efpeglenatide | 0.865 | 0.35         | 2.11         | 0.86    | 0.000    |
| EXSCEL         | Tirzepatide vs Exenatide     | NA    | NA           | NA           | 0.81    | NA       |
| EXSCEL         | Tirzepatide vs Liraglutide   | 0.777 | 0.36         | 1.67         | 0.78    | 0.000    |
| EXSCEL         | Tirzepatide vs Lixisenatide  | 0.618 | 0.27         | 1.39         | 0.62    | 0.000    |

|           |                              |       |      |      |      |        |
|-----------|------------------------------|-------|------|------|------|--------|
| EXSCEL    | Tirzepatide vs Semaglutide   | 0.792 | 0.40 | 1.57 | 0.79 | 0.000  |
| FLOW      | Tirzepatide vs Placebo       | 0.692 | 0.45 | 1.06 | 0.69 | 0.000  |
| FLOW      | Tirzepatide vs Dulaglutide   | 0.910 | 0.68 | 1.21 | 0.91 | 0.000  |
| FLOW      | Tirzepatide vs Efpeglenatide | 0.865 | 0.43 | 1.74 | 0.86 | 0.000  |
| FLOW      | Tirzepatide vs Exenatide     | 0.814 | 0.48 | 1.37 | 0.81 | 0.000  |
| FLOW      | Tirzepatide vs Liraglutide   | 0.777 | 0.46 | 1.32 | 0.78 | 0.000  |
| FLOW      | Tirzepatide vs Lixisenatide  | 0.618 | 0.34 | 1.12 | 0.62 | 0.000  |
| FLOW      | Tirzepatide vs Semaglutide   | 0.876 | 0.53 | 1.44 | 0.79 | 0.084  |
| LEADER    | Tirzepatide vs Placebo       | 0.692 | 0.37 | 1.29 | 0.69 | 0.000  |
| LEADER    | Tirzepatide vs Dulaglutide   | 0.910 | 0.59 | 1.40 | 0.91 | 0.000  |
| LEADER    | Tirzepatide vs Efpeglenatide | 0.865 | 0.35 | 2.11 | 0.86 | 0.000  |
| LEADER    | Tirzepatide vs Exenatide     | 0.814 | 0.38 | 1.74 | 0.81 | 0.000  |
| LEADER    | Tirzepatide vs Liraglutide   | NA    | NA   | NA   | 0.78 | NA     |
| LEADER    | Tirzepatide vs Lixisenatide  | 0.618 | 0.27 | 1.39 | 0.62 | 0.000  |
| LEADER    | Tirzepatide vs Semaglutide   | 0.792 | 0.40 | 1.57 | 0.79 | 0.000  |
| PIONEER 6 | Tirzepatide vs Placebo       | 0.692 | 0.33 | 1.44 | 0.69 | 0.000  |
| PIONEER 6 | Tirzepatide vs Dulaglutide   | 0.910 | 0.55 | 1.51 | 0.91 | 0.000  |
| PIONEER 6 | Tirzepatide vs Efpeglenatide | 0.865 | 0.32 | 2.37 | 0.86 | 0.000  |
| PIONEER 6 | Tirzepatide vs Exenatide     | 0.814 | 0.33 | 1.99 | 0.81 | 0.000  |
| PIONEER 6 | Tirzepatide vs Liraglutide   | 0.777 | 0.32 | 1.91 | 0.78 | 0.000  |
| PIONEER 6 | Tirzepatide vs Lixisenatide  | 0.618 | 0.24 | 1.58 | 0.62 | 0.000  |
| PIONEER 6 | Tirzepatide vs Semaglutide   | 0.778 | 0.35 | 1.74 | 0.79 | -0.013 |
| REWIND    | Tirzepatide vs Placebo       | NA    | NA   | NA   | 0.69 | NA     |
| REWIND    | Tirzepatide vs Dulaglutide   | NA    | NA   | NA   | 0.91 | NA     |
| REWIND    | Tirzepatide vs Efpeglenatide | NA    | NA   | NA   | 0.86 | NA     |
| REWIND    | Tirzepatide vs Exenatide     | NA    | NA   | NA   | 0.81 | NA     |
| REWIND    | Tirzepatide vs Liraglutide   | NA    | NA   | NA   | 0.78 | NA     |

|                     |                              |       |      |      |      |        |
|---------------------|------------------------------|-------|------|------|------|--------|
| <b>REWIND</b>       | Tirzepatide vs Lixisenatide  | NA    | NA   | NA   | 0.62 | NA     |
| <b>REWIND</b>       | Tirzepatide vs Semaglutide   | NA    | NA   | NA   | 0.79 | NA     |
| <b>SOUL</b>         | Tirzepatide vs Placebo       | 0.692 | 0.27 | 1.76 | 0.69 | 0.000  |
| <b>SOUL</b>         | Tirzepatide vs Dulaglutide   | 0.910 | 0.47 | 1.75 | 0.91 | 0.000  |
| <b>SOUL</b>         | Tirzepatide vs Efpeglenatide | 0.865 | 0.25 | 2.97 | 0.86 | 0.000  |
| <b>SOUL</b>         | Tirzepatide vs Exenatide     | 0.814 | 0.26 | 2.55 | 0.81 | 0.000  |
| <b>SOUL</b>         | Tirzepatide vs Liraglutide   | 0.777 | 0.25 | 2.45 | 0.78 | 0.000  |
| <b>SOUL</b>         | Tirzepatide vs Lixisenatide  | 0.618 | 0.19 | 2.01 | 0.62 | 0.000  |
| <b>SOUL</b>         | Tirzepatide vs Semaglutide   | 0.814 | 0.29 | 2.32 | 0.79 | 0.022  |
| <b>SURPASS CVOT</b> | Tirzepatide vs Placebo       | NA    | NA   | NA   | 0.69 | NA     |
| <b>SURPASS CVOT</b> | Tirzepatide vs Dulaglutide   | NA    | NA   | NA   | 0.91 | NA     |
| <b>SURPASS CVOT</b> | Tirzepatide vs Efpeglenatide | NA    | NA   | NA   | 0.86 | NA     |
| <b>SURPASS CVOT</b> | Tirzepatide vs Exenatide     | NA    | NA   | NA   | 0.81 | NA     |
| <b>SURPASS CVOT</b> | Tirzepatide vs Liraglutide   | NA    | NA   | NA   | 0.78 | NA     |
| <b>SURPASS CVOT</b> | Tirzepatide vs Lixisenatide  | NA    | NA   | NA   | 0.62 | NA     |
| <b>SURPASS CVOT</b> | Tirzepatide vs Semaglutide   | NA    | NA   | NA   | 0.79 | NA     |
| <b>SUSTAIN 6</b>    | Tirzepatide vs Placebo       | 0.692 | 0.44 | 1.08 | 0.69 | 0.000  |
| <b>SUSTAIN 6</b>    | Tirzepatide vs Dulaglutide   | 0.910 | 0.67 | 1.23 | 0.91 | 0.000  |
| <b>SUSTAIN 6</b>    | Tirzepatide vs Efpeglenatide | 0.865 | 0.42 | 1.77 | 0.86 | 0.000  |
| <b>SUSTAIN 6</b>    | Tirzepatide vs Exenatide     | 0.814 | 0.47 | 1.40 | 0.81 | 0.000  |
| <b>SUSTAIN 6</b>    | Tirzepatide vs Liraglutide   | 0.777 | 0.45 | 1.35 | 0.78 | 0.000  |
| <b>SUSTAIN 6</b>    | Tirzepatide vs Lixisenatide  | 0.618 | 0.33 | 1.14 | 0.62 | 0.000  |
| <b>SUSTAIN 6</b>    | Tirzepatide vs Semaglutide   | 0.720 | 0.43 | 1.20 | 0.79 | -0.072 |

Supplemental Table S24. Leave-one-out sensitivity analysis at the agent-level for non-fatal stroke comparing tirzepatide versus placebo, presenting hazard ratios with 95% confidence intervals after sequential removal of each individual trial.

## Certainty of evidence (GRADE) using Confidence in Network Meta-Analysis (CINeMA) for the class-level network meta-analysis

| Outcome             | Comparison (HR, 95% CI)                     | Direct comps (n) | Within-study bias | Reporting bias | Indirectness                                            | Imprecision                                    | Heterogeneity                     | Incoherence     | Confidence rating |
|---------------------|---------------------------------------------|------------------|-------------------|----------------|---------------------------------------------------------|------------------------------------------------|-----------------------------------|-----------------|-------------------|
| MACE                | Tirzepatide vs placebo (HR 0.79, 0.69-0.91) | 0                | No concerns       | No concerns    | Some concerns (indirect-only; potential intransitivity) | No concerns                                    | Some concerns ( $I^2 = 31.38\%$ ) | Not assessable* | Low               |
| MACE                | GLP-1RA vs placebo (HR 0.86, 0.82-0.91)     | 10               | No concerns       | No concerns    | No concerns                                             | No concerns                                    | Some concerns ( $I^2 = 31.38\%$ ) | Not assessable* | Moderate          |
| CV mortality        | Tirzepatide vs placebo (HR 0.77, 0.66-0.90) | 0                | No concerns       | No concerns    | Some concerns (indirect-only; potential intransitivity) | No concerns                                    | No concerns ( $I^2 = 23.5\%$ )    | Not assessable* | Low               |
| CV mortality        | GLP-1RA vs placebo (HR 0.87, 0.81-0.92)     | 10               | No concerns       | No concerns    | No concerns                                             | No concerns                                    | No concerns ( $I^2 = 23.5\%$ )    | Not assessable* | High              |
| All-cause mortality | Tirzepatide vs placebo (HR 0.74, 0.65-0.83) | 0                | No concerns       | No concerns    | Some concerns (indirect-only; potential intransitivity) | No concerns                                    | No concerns ( $I^2 = 2.76\%$ )    | Not assessable* | Low               |
| All-cause mortality | GLP-1RA vs placebo (HR 0.88, 0.83-0.92)     | 10               | No concerns       | No concerns    | No concerns                                             | No concerns                                    | No concerns ( $I^2 = 2.76\%$ )    | Not assessable* | High              |
| Non-fatal MI        | Tirzepatide vs placebo (HR 0.77, 0.61-0.97) | 0                | No concerns       | No concerns    | Some concerns (indirect-only; potential intransitivity) | Some concerns (CI close to 1; relatively wide) | Some concerns ( $I^2 = 31.09\%$ ) | Not assessable* | Low               |
| Non-fatal MI        | GLP-1RA vs placebo (HR 0.90, 0.82-0.98)     | 9                | No concerns       | No concerns    | No concerns                                             | Some concerns (CI close to 1)                  | Some concerns ( $I^2 = 31.09\%$ ) | Not assessable* | Moderate          |
| Non-fatal stroke    | Tirzepatide vs placebo (HR 0.79, 0.64-0.97) | 0                | No concerns       | No concerns    | Some concerns (indirect-only; potential intransitivity) | Some concerns (CI close to 1)                  | No concerns ( $I^2 = 12.85\%$ )   | Not assessable* | Low               |
| Non-fatal stroke    | GLP-1RA vs placebo (HR 0.87, 0.79-0.95)     | 9                | No concerns       | No concerns    | No concerns                                             | No concerns                                    | No concerns ( $I^2 = 12.85\%$ )   | Not assessable* | High              |

Supplemental Table S25: Certainty of evidence for class-level network estimates was assessed using the CINeMA framework across key outcomes, with domain judgments and overall confidence ratings reported for each comparison. \* Incoherence was not assessable because there were insufficient data to contrast direct and indirect evidence for the same comparison.

## Certainty of evidence (GRADE) using Confidence in Network Meta-Analysis (CINeMA) for the agent-level network meta-analysis

| Outcome | Comparison (HR, 95% CI)                        | Direct comps (n) | Within-study bias | Reporting bias | Indirectness                   | Imprecision                   | Heterogeneity               | Incoherence     | Confidence rating |
|---------|------------------------------------------------|------------------|-------------------|----------------|--------------------------------|-------------------------------|-----------------------------|-----------------|-------------------|
| MACE    | Tirzepatide vs placebo (0.81, 0.70–0.94)       | 0                | No concerns       | No concerns    | Major concerns (indirect-only) | No concerns                   | No concerns ( $I^2 = 0\%$ ) | Not assessable* | Low               |
| MACE    | Albiglutide vs placebo (0.78, 0.68–0.90)       | 1                | No concerns       | No concerns    | No concerns                    | No concerns                   | No concerns ( $I^2 = 0\%$ ) | Not assessable* | High              |
| MACE    | Dulaglutide vs placebo (0.88, 0.79–0.98)       | 1                | No concerns       | No concerns    | No concerns                    | No concerns                   | No concerns ( $I^2 = 0\%$ ) | Not assessable* | High              |
| MACE    | Efpeglenatide vs placebo (0.73, 0.58–0.92)     | 1                | No concerns       | No concerns    | No concerns                    | Some concerns (wide CI)       | No concerns ( $I^2 = 0\%$ ) | Not assessable* | Moderate          |
| MACE    | Exenatide vs placebo (0.91, 0.83–1.00)         | 1                | No concerns       | No concerns    | No concerns                    | Some concerns (borderline CI) | No concerns ( $I^2 = 0\%$ ) | Not assessable* | Moderate          |
| MACE    | Liraglutide vs placebo (0.87, 0.78–0.97)       | 1                | No concerns       | No concerns    | No concerns                    | No concerns                   | No concerns ( $I^2 = 0\%$ ) | Not assessable* | High              |
| MACE    | Lixisenatide vs placebo (1.02, 0.89–1.17)      | 1                | No concerns       | No concerns    | No concerns                    | Some concerns (CI crosses 1)  | No concerns ( $I^2 = 0\%$ ) | Not assessable* | Moderate          |
| MACE    | Semaglutide vs placebo (0.83, 0.76–0.91)       | 4                | No concerns       | No concerns    | No concerns                    | No concerns                   | No concerns ( $I^2 = 0\%$ ) | Not assessable* | High              |
| MACE    | Tirzepatide vs Albiglutide (1.04, 0.85–1.27)   | 0                | No concerns       | No concerns    | Major concerns (indirect-only) | Some concerns (CI crosses 1)  | No concerns ( $I^2 = 0\%$ ) | Not assessable* | Very low          |
| MACE    | Tirzepatide vs Dulaglutide (0.92, 0.83–1.07)   | 1                | No concerns       | No concerns    | No concerns                    | Some concerns (CI crosses 1)  | No concerns ( $I^2 = 0\%$ ) | Not assessable* | Low               |
| MACE    | Tirzepatide vs Efpeglenatide (1.11, 0.84–1.46) | 0                | No concerns       | No concerns    | Major concerns (indirect-only) | Some concerns (CI crosses 1)  | No concerns ( $I^2 = 0\%$ ) | Not assessable* | Very low          |
| MACE    | Tirzepatide vs Exenatide (0.89, 0.75–1.06)     | 0                | No concerns       | No concerns    | Major concerns (indirect-only) | Some concerns (CI crosses 1)  | No concerns ( $I^2 = 0\%$ ) | Not assessable* | Very low          |
| MACE    | Tirzepatide vs Liraglutide (0.93, 0.78–1.12)   | 0                | No concerns       | No concerns    | Major concerns (indirect-only) | Some concerns (CI crosses 1)  | No concerns ( $I^2 = 0\%$ ) | Not assessable* | Very low          |

|              |                                                |   |             |             |                                |                               |                                   |                 |          |
|--------------|------------------------------------------------|---|-------------|-------------|--------------------------------|-------------------------------|-----------------------------------|-----------------|----------|
| MACE         | Tirzepatide vs Lixisenatide (0.79, 0.65–0.97)  | 0 | No concerns | No concerns | Major concerns (indirect-only) | No concerns                   | No concerns ( $I^2 = 0\%$ )       | Not assessable* | Low      |
| MACE         | Tirzepatide vs Semaglutide (0.97, 0.82–1.15)   | 0 | No concerns | No concerns | Major concerns (indirect-only) | Some concerns (CI crosses 1)  | No concerns ( $I^2 = 0\%$ )       | Not assessable* | Very low |
| CV mortality | Tirzepatide vs placebo (0.81, 0.50–1.32)       | 0 | No concerns | No concerns | Major concerns (indirect-only) | Some concerns (wide CI)       | Some concerns ( $I^2 = 58.85\%$ ) | Not assessable* | Very low |
| CV mortality | Albiglutide vs placebo (0.93, 0.62–1.39)       | 1 | No concerns | No concerns | No concerns                    | Some concerns (wide CI)       | Some concerns ( $I^2 = 58.85\%$ ) | Not assessable* | Low      |
| CV mortality | Dulaglutide vs placebo (0.91, 0.64–1.29)       | 1 | No concerns | No concerns | No concerns                    | Some concerns (wide CI)       | Some concerns ( $I^2 = 58.85\%$ ) | Not assessable* | Low      |
| CV mortality | Efpeglenatide vs placebo (0.72, 0.45–1.16)     | 1 | No concerns | No concerns | No concerns                    | Some concerns (wide CI)       | Some concerns ( $I^2 = 58.85\%$ ) | Not assessable* | Low      |
| CV mortality | Exenatide vs placebo (0.88, 0.62–1.25)         | 1 | No concerns | No concerns | No concerns                    | Some concerns (wide CI)       | Some concerns ( $I^2 = 58.85\%$ ) | Not assessable* | Low      |
| CV mortality | Liraglutide vs placebo (0.78, 0.54–1.12)       | 1 | No concerns | No concerns | No concerns                    | Some concerns (CI crosses 1)  | Some concerns ( $I^2 = 58.85\%$ ) | Not assessable* | Low      |
| CV mortality | Lixisenatide vs placebo (0.98, 0.66–1.45)      | 1 | No concerns | No concerns | No concerns                    | Some concerns (wide CI)       | Some concerns ( $I^2 = 58.85\%$ ) | Not assessable* | Low      |
| CV mortality | Semaglutide vs placebo (0.81, 0.65–1.00)       | 4 | No concerns | No concerns | No concerns                    | Some concerns (borderline CI) | Some concerns ( $I^2 = 58.85\%$ ) | Not assessable* | Low      |
| CV mortality | Tirzepatide vs Albiglutide (1.15, 0.61–2.16)   | 0 | No concerns | No concerns | Major concerns (indirect-only) | Major concerns (very wide CI) | Some concerns ( $I^2 = 58.85\%$ ) | Not assessable* | Very low |
| CV mortality | Tirzepatide vs Dulaglutide (1.12, 0.80–1.59)   | 1 | No concerns | No concerns | No concerns                    | Some concerns (CI crosses 1)  | Some concerns ( $I^2 = 58.85\%$ ) | Not assessable* | Very low |
| CV mortality | Tirzepatide vs Efpeglenatide (0.89, 0.45–1.77) | 0 | No concerns | No concerns | Major concerns (indirect-only) | Major concerns (very wide CI) | Some concerns ( $I^2 = 58.85\%$ ) | Not assessable* | Very low |
| CV mortality | Tirzepatide vs Exenatide (0.92, 0.50–1.68)     | 0 | No concerns | No concerns | Major concerns (indirect-only) | Major concerns (very wide CI) | Some concerns ( $I^2 = 58.85\%$ ) | Not assessable* | Very low |
| CV mortality | Tirzepatide vs Liraglutide (1.04, 0.56–1.91)   | 0 | No concerns | No concerns | Major concerns (indirect-only) | Major concerns (very wide CI) | Some concerns ( $I^2 = 58.85\%$ ) | Not assessable* | Very low |

|                     |                                                |   |             |             |                                |                               |                                   |                 |          |
|---------------------|------------------------------------------------|---|-------------|-------------|--------------------------------|-------------------------------|-----------------------------------|-----------------|----------|
| CV mortality        | Tirzepatide vs Lixisenatide (0.83, 0.44–1.55)  | 0 | No concerns | No concerns | Major concerns (indirect-only) | Major concerns (very wide CI) | Some concerns ( $I^2 = 58.85\%$ ) | Not assessable* | Very low |
| CV mortality        | Tirzepatide vs Semaglutide (1.01, 0.59–1.72)   | 0 | No concerns | No concerns | Major concerns (indirect-only) | Major concerns (very wide CI) | Some concerns ( $I^2 = 58.85\%$ ) | Not assessable* | Very low |
| All-cause mortality | Tirzepatide vs placebo (0.76, 0.56–1.03)       | 0 | No concerns | No concerns | Major concerns (indirect-only) | Some concerns (CI crosses 1)  | Some concerns ( $I^2 = 56.57\%$ ) | Not assessable* | Very low |
| All-cause mortality | Albiglutide vs placebo (0.95, 0.73–1.24)       | 1 | No concerns | No concerns | No concerns                    | Some concerns (CI crosses 1)  | Some concerns ( $I^2 = 56.57\%$ ) | Not assessable* | Low      |
| All-cause mortality | Dulaglutide vs placebo (0.90, 0.72–1.12)       | 1 | No concerns | No concerns | No concerns                    | Some concerns (CI crosses 1)  | Some concerns ( $I^2 = 56.57\%$ ) | Not assessable* | Low      |
| All-cause mortality | Efpeglenatide vs placebo (0.78, 0.55–1.11)     | 1 | No concerns | No concerns | No concerns                    | Some concerns (CI crosses 1)  | Some concerns ( $I^2 = 56.57\%$ ) | Not assessable* | Low      |
| All-cause mortality | Exenatide vs placebo (0.86, 0.69–1.07)         | 1 | No concerns | No concerns | No concerns                    | Some concerns (CI crosses 1)  | Some concerns ( $I^2 = 56.57\%$ ) | Not assessable* | Low      |
| All-cause mortality | Liraglutide vs placebo (0.85, 0.68–1.07)       | 1 | No concerns | No concerns | No concerns                    | Some concerns (CI crosses 1)  | Some concerns ( $I^2 = 56.57\%$ ) | Not assessable* | Low      |
| All-cause mortality | Lixisenatide vs placebo (0.94, 0.72–1.22)      | 1 | No concerns | No concerns | No concerns                    | Some concerns (CI crosses 1)  | Some concerns ( $I^2 = 56.57\%$ ) | Not assessable* | Low      |
| All-cause mortality | Semaglutide vs placebo (0.85, 0.73–0.99)       | 4 | No concerns | No concerns | No concerns                    | Some concerns (borderline CI) | Some concerns ( $I^2 = 56.57\%$ ) | Not assessable* | Low      |
| All-cause mortality | Tirzepatide vs Albiglutide (0.80, 0.53–1.20)   | 0 | No concerns | No concerns | Major concerns (indirect-only) | Major concerns (wide CI)      | Some concerns ( $I^2 = 56.57\%$ ) | Not assessable* | Very low |
| All-cause mortality | Tirzepatide vs Dulaglutide (0.84, 0.68–1.04)   | 1 | No concerns | No concerns | No concerns                    | Some concerns (CI crosses 1)  | Some concerns ( $I^2 = 56.57\%$ ) | Not assessable* | Very low |
| All-cause mortality | Tirzepatide vs Efpeglenatide (0.97, 0.61–1.54) | 0 | No concerns | No concerns | Major concerns (indirect-only) | Major concerns (wide CI)      | Some concerns ( $I^2 = 56.57\%$ ) | Not assessable* | Very low |
| All-cause mortality | Tirzepatide vs Exenatide (0.88, 0.60–1.28)     | 0 | No concerns | No concerns | Major concerns (indirect-only) | Major concerns (wide CI)      | Some concerns ( $I^2 = 56.57\%$ ) | Not assessable* | Very low |
| All-cause mortality | Tirzepatide vs Liraglutide (0.89, 0.61–1.31)   | 0 | No concerns | No concerns | Major concerns (indirect-only) | Major concerns (wide CI)      | Some concerns ( $I^2 = 56.57\%$ ) | Not assessable* | Very low |

|                     |                                                |   |             |             |                                |                               |                                   |                 |          |
|---------------------|------------------------------------------------|---|-------------|-------------|--------------------------------|-------------------------------|-----------------------------------|-----------------|----------|
| All-cause mortality | Tirzepatide vs Lixisenatide (0.80, 0.54–1.20)  | 0 | No concerns | No concerns | Major concerns (indirect-only) | Major concerns (wide CI)      | Some concerns ( $I^2 = 56.57\%$ ) | Not assessable* | Very low |
| All-cause mortality | Tirzepatide vs Semaglutide (0.89, 0.63–1.25)   | 0 | No concerns | No concerns | Major concerns (indirect-only) | Some concerns (CI crosses 1)  | Some concerns ( $I^2 = 56.57\%$ ) | Not assessable* | Very low |
| Non-fatal MI        | Tirzepatide vs placebo (0.83, 0.65–1.05)       | 0 | No concerns | No concerns | Major concerns (indirect-only) | Some concerns (CI crosses 1)  | No concerns ( $I^2 = 8.21\%$ )    | Not assessable* | Very low |
| Non-fatal MI        | Dulaglutide vs placebo (0.96, 0.79–1.16)       | 1 | No concerns | No concerns | No concerns                    | Some concerns (CI crosses 1)  | No concerns ( $I^2 = 8.21\%$ )    | Not assessable* | Moderate |
| Non-fatal MI        | Efpeglenatide vs placebo (0.78, 0.55–1.10)     | 1 | No concerns | No concerns | No concerns                    | Some concerns (CI crosses 1)  | No concerns ( $I^2 = 8.21\%$ )    | Not assessable* | Moderate |
| Non-fatal MI        | Exenatide vs placebo (0.97, 0.85–1.10)         | 1 | No concerns | No concerns | No concerns                    | Some concerns (CI crosses 1)  | No concerns ( $I^2 = 8.21\%$ )    | Not assessable* | Moderate |
| Non-fatal MI        | Liraglutide vs placebo (0.88, 0.75–1.03)       | 1 | No concerns | No concerns | No concerns                    | Some concerns (CI crosses 1)  | No concerns ( $I^2 = 8.21\%$ )    | Not assessable* | Moderate |
| Non-fatal MI        | Lixisenatide vs placebo (1.03, 0.87–1.22)      | 1 | No concerns | No concerns | No concerns                    | Some concerns (CI crosses 1)  | No concerns ( $I^2 = 8.21\%$ )    | Not assessable* | Moderate |
| Non-fatal MI        | Semaglutide vs placebo (0.78, 0.68–0.91)       | 4 | No concerns | No concerns | No concerns                    | No concerns                   | No concerns ( $I^2 = 8.21\%$ )    | Not assessable* | High     |
| Non-fatal MI        | Tirzepatide vs Dulaglutide (0.86, 0.74–1.00)   | 1 | No concerns | No concerns | No concerns                    | Some concerns (borderline CI) | No concerns ( $I^2 = 8.21\%$ )    | Not assessable* | Low      |
| Non-fatal MI        | Tirzepatide vs Efpeglenatide (1.06, 0.69–1.62) | 0 | No concerns | No concerns | Major concerns (indirect-only) | Major concerns (wide CI)      | No concerns ( $I^2 = 8.21\%$ )    | Not assessable* | Very low |
| Non-fatal MI        | Tirzepatide vs Exenatide (0.85, 0.65–1.12)     | 0 | No concerns | No concerns | Major concerns (indirect-only) | Some concerns (CI crosses 1)  | No concerns ( $I^2 = 8.21\%$ )    | Not assessable* | Very low |
| Non-fatal MI        | Tirzepatide vs Liraglutide (0.94, 0.70–1.26)   | 0 | No concerns | No concerns | Major concerns (indirect-only) | Some concerns (CI crosses 1)  | No concerns ( $I^2 = 8.21\%$ )    | Not assessable* | Very low |
| Non-fatal MI        | Tirzepatide vs Lixisenatide (0.80, 0.60–1.08)  | 0 | No concerns | No concerns | Major concerns (indirect-only) | Some concerns (CI crosses 1)  | No concerns ( $I^2 = 8.21\%$ )    | Not assessable* | Very low |
| Non-fatal MI        | Tirzepatide vs Semaglutide (1.06, 0.79–1.40)   | 0 | No concerns | No concerns | Major concerns (indirect-only) | Some concerns (CI crosses 1)  | No concerns ( $I^2 = 8.21\%$ )    | Not assessable* | Very low |

|                  |                                                |   |             |             |                                |                               |                                   |                 |          |
|------------------|------------------------------------------------|---|-------------|-------------|--------------------------------|-------------------------------|-----------------------------------|-----------------|----------|
| Non-fatal stroke | Tirzepatide vs placebo (0.69, 0.37–1.29)       | 0 | No concerns | No concerns | Major concerns (indirect-only) | Major concerns (very wide CI) | Some concerns ( $I^2 = 44.81\%$ ) | Not assessable* | Very low |
| Non-fatal stroke | Dulaglutide vs placebo (0.76, 0.49–1.19)       | 1 | No concerns | No concerns | No concerns                    | Some concerns (CI crosses 1)  | Some concerns ( $I^2 = 44.81\%$ ) | Not assessable* | Moderate |
| Non-fatal stroke | Efpeglenatide vs placebo (0.80, 0.42–1.52)     | 1 | No concerns | No concerns | No concerns                    | Major concerns (very wide CI) | Some concerns ( $I^2 = 44.81\%$ ) | Not assessable* | Low      |
| Non-fatal stroke | Exenatide vs placebo (0.85, 0.55–1.31)         | 1 | No concerns | No concerns | No concerns                    | Some concerns (CI crosses 1)  | Some concerns ( $I^2 = 44.81\%$ ) | Not assessable* | Moderate |
| Non-fatal stroke | Liraglutide vs placebo (0.89, 0.57–1.39)       | 1 | No concerns | No concerns | No concerns                    | Some concerns (CI crosses 1)  | Some concerns ( $I^2 = 44.81\%$ ) | Not assessable* | Moderate |
| Non-fatal stroke | Lixisenatide vs placebo (1.12, 0.66–1.89)      | 1 | No concerns | No concerns | No concerns                    | Major concerns (very wide CI) | Some concerns ( $I^2 = 44.81\%$ ) | Not assessable* | Low      |
| Non-fatal stroke | Semaglutide vs placebo (0.87, 0.66–1.16)       | 4 | No concerns | No concerns | No concerns                    | Some concerns (CI crosses 1)  | Some concerns ( $I^2 = 44.81\%$ ) | Not assessable* | Moderate |
| Non-fatal stroke | Tirzepatide vs Dulaglutide (0.91, 0.59–1.40)   | 1 | No concerns | No concerns | No concerns                    | Some concerns (wide CI)       | Some concerns ( $I^2 = 44.81\%$ ) | Not assessable* | Low      |
| Non-fatal stroke | Tirzepatide vs Efpeglenatide (0.86, 0.35–2.11) | 0 | No concerns | No concerns | Major concerns (indirect-only) | Major concerns (very wide CI) | Some concerns ( $I^2 = 44.81\%$ ) | Not assessable* | Very low |
| Non-fatal stroke | Tirzepatide vs Exenatide (0.81, 0.38–1.74)     | 0 | No concerns | No concerns | Major concerns (indirect-only) | Major concerns (very wide CI) | Some concerns ( $I^2 = 44.81\%$ ) | Not assessable* | Very low |
| Non-fatal stroke | Tirzepatide vs Liraglutide (0.78, 0.36–1.67)   | 0 | No concerns | No concerns | Major concerns (indirect-only) | Major concerns (very wide CI) | Some concerns ( $I^2 = 44.81\%$ ) | Not assessable* | Very low |
| Non-fatal stroke | Tirzepatide vs Lixisenatide (0.62, 0.27–1.39)  | 0 | No concerns | No concerns | Major concerns (indirect-only) | Major concerns (very wide CI) | Some concerns ( $I^2 = 44.81\%$ ) | Not assessable* | Very low |
| Non-fatal stroke | Tirzepatide vs Semaglutide (0.79, 0.40–1.57)   | 0 | No concerns | No concerns | Major concerns (indirect-only) | Major concerns (very wide CI) | Some concerns ( $I^2 = 44.81\%$ ) | Not assessable* | Very low |

Supplemental Table S26: Certainty of evidence for agent-level network estimates was assessed using the CINeMA framework across key outcomes, with domain judgments and overall confidence ratings reported for each comparison. \* Incoherence was not assessable because there were insufficient data to contrast direct and indirect evidence for the same comparison.