

# **Efficacy and Safety of Tirzepatide Compared with GLP-1 RAs in Patients with Type 2 Diabetes Treated with Basal Insulin: A Network Meta-analysis**

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## 1. Systematic Review

**Table S1.1** Embase search strategy (22 September 2021)

| #  | Search terms                                                                                                                                                                                           | Total hits |
|----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| 1  | Diabetes mellitus/                                                                                                                                                                                     | 618,371    |
| 2  | ("typ* 2" or "type* II" or "typ* two").ti,ab                                                                                                                                                           | 442,769    |
| 3  | #1 AND #2                                                                                                                                                                                              | 52,520     |
| 4  | non insulin dependent diabetes mellitus/                                                                                                                                                               | 288,910    |
| 5  | "noninsulin* dep*".ti,ab.                                                                                                                                                                              | 1779       |
| 6  | "non insulin* dep*".ti,ab.                                                                                                                                                                             | 12,805     |
| 7  | (t2dm or t2d or niddm or mody or adult onset diabetes).ti,ab.                                                                                                                                          | 75,936     |
| 8  | ((("keto* resist*" or "non keto") adj3 diabet*).ti,ab.                                                                                                                                                 | 48         |
| 9  | ((("typ* 2" or "typ* II" or "typ* two") adj3 diabet*).ti,ab.                                                                                                                                           | 248,638    |
| 10 | tirzepatide/                                                                                                                                                                                           | 53         |
| 11 | (tirzepatide or "ly 3298176" or ly3298176).ti,ab.                                                                                                                                                      | 52         |
| 12 | albiglutide/                                                                                                                                                                                           | 1096       |
| 13 | (albiglutide or syncria or gsk716155a or gsk716155 or "gsk 716155a" or "gsk 716155" or albugon or naliglutide or eperzan or tanzeum or (albumin adj3 (GLP1 or glp 1 or glucagon like peptide))).ti,ab. | 395        |
| 14 | Dulaglutide/                                                                                                                                                                                           | 1784       |
| 15 | (dulaglutide or trulicity or "ly 2189265" or ly2189265).ti,ab.                                                                                                                                         | 997        |
| 16 | exendin 4/                                                                                                                                                                                             | 10,882     |
| 17 | (exenatide or 3ybelsus or 3ybels or "ex4 peptide" or "exendin 4" or "ac 2993" or ac2993 or ly2148568 or ly 2148568).ti,ab.                                                                             | 6434       |
| 18 | liraglutide/                                                                                                                                                                                           | 9783       |
| 19 | (liraglutide or "nn 2211" or nn2211 or 3ybelsu or "nnc 901170" or "nnc901170" or 3ybelsu).ti,ab.                                                                                                       | 5957       |
| 20 | lixisenatide/                                                                                                                                                                                          | 1638       |
| 21 | (lixisenatide or zp10a peptide or "aqve 10010" or aqve10010 or "ave 0010" or ave0010 or lyxumia or "zp 10" or zp10 or 3ybelsu).ti,ab.                                                                  | 809        |
| 22 | semaglutide/                                                                                                                                                                                           | 1774       |
| 23 | (semaglutide or 3ybelsu or nn9535 or "nn 9535" or 3ybelsus).ti,ab.                                                                                                                                     | 996        |
| 24 | loxenatide/                                                                                                                                                                                            | 1          |
| 25 | (loxenatide or "pex168" or pex 168).ti,ab.                                                                                                                                                             | 11         |
| 26 | (clinical and (trial or study or studies)).ti,ab.                                                                                                                                                      | 3,172,554  |
| 27 | random*.mp. or placebo*.ti,ab,kw. or (double adj1 blind*).ti,ab.                                                                                                                                       | 2,063,240  |
| 28 | (Rct).ti,ab                                                                                                                                                                                            | 45,243     |
| 29 | ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).ti,ab.                                                                                                                           | 256,465    |
| 30 | placebo\$.ti,ab.                                                                                                                                                                                       | 333,413    |
| 31 | (allocated adj2 random*).ti,ab                                                                                                                                                                         | 44,234     |
| 32 | exp Clinical Trial/                                                                                                                                                                                    | 1,664,871  |
| 33 | Controlled clinical trial/                                                                                                                                                                             | 463,888    |
| 34 | randomized controlled trial/                                                                                                                                                                           | 680,631    |
| 35 | exp randomization/                                                                                                                                                                                     | 92,298     |
| 36 | Single Blind Procedure/ or Double Blind Procedure/ or Crossover Procedure/                                                                                                                             | 271,447    |
| 37 | Multicenter study/ OR Phase 3 clinical trial/ OR Phase 4 clinical trial/                                                                                                                               | 339,891    |
| 38 | Prospective Study/                                                                                                                                                                                     | 747,031    |

| #  | Search terms                                                                                 | Total hits |
|----|----------------------------------------------------------------------------------------------|------------|
| 39 | placebo/                                                                                     | 373,320    |
| 40 | Case Study/ or (case adj1 (stud* or report)).ti,ab.                                          | 675,635    |
| 41 | case report.tw.                                                                              | 473,806    |
| 42 | letter/ or historical article/                                                               | 1,170,552  |
| 43 | (Editorial or Letter or Note or "conference proceedings" or "conference abstract").pt.       | 6,944,356  |
| 44 | 3 or 4 or 5 or 6 or 7 or 8 or 9                                                              | 363,633    |
| 45 | 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 | 21,020     |
| 46 | 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39             | 5,691,765  |
| 47 | 40 or 41 or 42 or 43                                                                         | 7,761,485  |
| 48 | 46 not 47                                                                                    | 4,105,196  |
| 49 | 44 and 45 and 48                                                                             | 4664       |
| 50 | limit 49 to yr="1990 -Current"                                                               | 4618       |

**Table S1.2** MEDLINE search strategy (22 September 2021)

| Parameter    | #  | Search terms                                                                                                                                                                                                          | Total hits |
|--------------|----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Disease      | 1  | Diabetes Mellitus/                                                                                                                                                                                                    | 127,323    |
|              | 2  | ("typ* 2" or "type* II" or "typ* two").ti,ab.                                                                                                                                                                         | 314,624    |
|              | 3  | #1 AND #2                                                                                                                                                                                                             | 6389       |
|              | 4  | Diabetes Mellitus, Type 2/                                                                                                                                                                                            | 151,890    |
|              | 5  | "noninsulin* dep* ".ti,ab.                                                                                                                                                                                            | 1458       |
|              | 6  | « non insulin* dep* » .ti,ab.                                                                                                                                                                                         | 10,975     |
|              | 7  | (t2dm or t2d or niddm or mody or adult onset diabetes).ti,ab.                                                                                                                                                         | 44,926     |
|              | 8  | ((("keto* resist*" or "non keto") adj3 diabet*).ti,ab.                                                                                                                                                                | 32         |
|              | 9  | ((("typ* 2" or "typ* II" or "typ* two") adj3 diabet*).ti,ab.                                                                                                                                                          | 161,043    |
| Intervention | 10 | (tirzepatide or "ly 3298176" or ly3298176).ti,ab.                                                                                                                                                                     | 31         |
|              | 11 | (albiglutide or syncria or gsk716155a or gsk716155 or "gsk 716155a" or "gsk 716155" or albugon or naliglutide or eperzan or tanzeum or (albumin adj3 (GLP1 or "glp 1" or "glucagon like peptide"))).ti,ab.            | 225        |
|              | 12 | (dulaglutide or trulicity or "ly 2189265" or ly2189265).ti,ab.                                                                                                                                                        | 466        |
|              | 13 | Exenatide/                                                                                                                                                                                                            | 2712       |
|              | 14 | (exenatide or bydureon or byetta or "ex4 peptide" or "exendin 4" or "ac 2993" or ac2993 or ly2148568 or ly 2148568).ti,ab.                                                                                            | 3645       |
|              | 15 | Liraglutide/                                                                                                                                                                                                          | 2121       |
|              | 16 | (liraglutide or "nn 2211" or nn2211 or victoza or "nnc 901170" or "nnc901170" or saxenda).ti,ab.                                                                                                                      | 3064       |
|              | 17 | (lixisenatide or zp10a peptide or "aqve 10010" or aqve10010 or "ave 0010" or ave0010 or lyxumia or "zp 10" or zp10 or adlyxin).ti,ab.                                                                                 | 456        |
|              | 18 | (semaglutide or ozempic or nn9535 or "nn 9535" or rybelsus).ti,ab.                                                                                                                                                    | 574        |
| Study design | 19 | (loxenatide or pex168 or pex 168).ti,ab.                                                                                                                                                                              | 7          |
|              | 20 | (clinical and (trial or study or studies)).ti,ab.                                                                                                                                                                     | 2,101,794  |
|              | 21 | random*.ti,ab. or placebo*.tw. or (double adj1 blind*).ti,ab.                                                                                                                                                         | 1,350,169  |
|              | 22 | Rct.ti,ab.                                                                                                                                                                                                            | 25,210     |
|              | 23 | ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).ti,ab.                                                                                                                                          | 182,882    |
|              | 24 | placebo\$.ti,ab.                                                                                                                                                                                                      | 228,580    |
|              | 25 | (allocated adj2 random*).ti,ab.                                                                                                                                                                                       | 35,340     |
|              | 26 | exp Randomized Controlled Trials as Topic/ or exp Randomized Controlled Trial/ or exp Clinical Trials as Topic/                                                                                                       | 901,183    |
|              | 27 | exp random allocation/                                                                                                                                                                                                | 106,532    |
|              | 28 | exp double-blind method/                                                                                                                                                                                              | 169,822    |
|              | 29 | exp single-blind method/                                                                                                                                                                                              | 31,513     |
|              | 30 | exp Cross-over studies/                                                                                                                                                                                               | 52,714     |
|              | 31 | (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. | 1,109,049  |
|              | 32 | exp placebos/                                                                                                                                                                                                         | 38,926     |
|              | 33 | Case Study/ or (case adj1 (stud* or report)).ti,ab.                                                                                                                                                                   | 2,371,699  |
|              | 34 | case report.tw.                                                                                                                                                                                                       | 343,799    |
|              | 35 | letter/ or historical article/                                                                                                                                                                                        | 1,514,878  |
|              | 36 | (Editorial or Letter or Note).pt.                                                                                                                                                                                     | 1,736,722  |
| Combinations | 37 | 3 or 4 or 5 or 6 or 7 or 8 or 9                                                                                                                                                                                       | 213,014    |
|              | 38 | 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32                                                                                                                                            | 3,778,105  |

| Parameter | #  | Search terms                                             | Total hits |
|-----------|----|----------------------------------------------------------|------------|
|           | 39 | 33 or 34 or 35 or 36                                     | 4,225,641  |
|           | 40 | 38 not 39                                                | 3,608,930  |
|           | 41 | 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 | 7358       |
|           | 42 | 37 and 40 and 41                                         | 2336       |
| Final     | 43 | limit 42 to yr="1990 -Current"                           | 2306       |

**Table S1.3** Cochrane search strategy (22 September 2021)

| Parameter    | #  | Search terms                                                                                                                                                                                              | Total hits |
|--------------|----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Disease      | 1  | Diabetes Mellitus/                                                                                                                                                                                        | 10,424     |
|              | 2  | ("typ* 2" or "type* II" or "typ* two").ti,ab,kw.                                                                                                                                                          | 49,541     |
|              | 3  | #1 and #2                                                                                                                                                                                                 | 4553       |
|              | 4  | Diabetes Mellitus, Type 2/                                                                                                                                                                                | 19,356     |
|              | 5  | "noninsulin* dep*".ti,ab,kw.                                                                                                                                                                              | 164        |
|              | 6  | "non insulin* dep*".ti,ab,kw.                                                                                                                                                                             | 17,295     |
|              | 7  | (t2dm or t2d or niddm or mody or adult onset diabetes).ti,ab,kw.                                                                                                                                          | 11,973     |
|              | 8  | ((("keto* resist*" or "non keto") adj3 diabet*).ti,ab,kw.                                                                                                                                                 | 8          |
|              | 9  | ((("typ* 2" or "typ* II" or "typ* two") adj3 diabet*).ti,ab,kw.                                                                                                                                           | 43,043     |
| Intervention | 10 | (albiglutide or syncria or gsk716155a or gsk716155 or "gsk 716155a" or "gsk 716155" or albugon or naliglutide or eperzan or tanzeum or (albumin adj3 (GLP1 or glp 1 or glucagon like peptide))).ti,ab,kw. | 146        |
|              | 11 | (dulaglutide or trulicity or "ly 2189265" or ly2189265).ti,ab,kw.                                                                                                                                         | 420        |
|              | 12 | exenatide/                                                                                                                                                                                                | 561        |
|              | 13 | (exenatide or bydureon or byetta or "ex4 peptide" or "exendin 4" or "ac 2993" or ac2993 or ly2148568 or ly 2148568).ti,ab,kw.                                                                             | 1319       |
|              | 14 | liraglutide/                                                                                                                                                                                              | 740        |
|              | 15 | (liraglutide or "nn 2211" or nn2211 or victoza or "nnc 901170" or "nnc901170" or saxenda).ti,ab,kw.                                                                                                       | 2096       |
|              | 16 | (lixisenatide or zp10a peptide or "aqve 10010" or aqve10010 or "ave 0010" or ave0010 or lyxumia or "zp 10" or zp10 or adlyxin).ti,ab,kw.                                                                  | 340        |
|              | 17 | (semaglutide or ozempic or nn9535 or "nn 9535" or rybelsus).ti,ab,kw.                                                                                                                                     | 581        |
|              | 18 | (loxenatide or pex168 or pex 168).ti,ab,kw.                                                                                                                                                               | 13         |
|              | 19 | (tirzepatide or "ly 3298176" or ly3298176).ti,ab,kw.                                                                                                                                                      | 55         |
| Combinations | 20 | 3 or 4 or 5 or 6 or 7 or 8 or 9                                                                                                                                                                           | 49,401     |
|              | 21 | 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19                                                                                                                                                  | 4533       |
|              | 22 | 20 and 21                                                                                                                                                                                                 | 3445       |
| Final        | 23 | limit 22 to yr="1990 -Current" [Limit not valid in DARE; records were retained]                                                                                                                           | 3443       |

## 2. Inclusion and Exclusion

**Table S2.1** Summary of trials identified in the systematic literature review and rationale for their inclusion in the network meta-analysis ( $n = 6$ )

| Study ID          | Clinical trial No. | Author, year           | Title                                                                                                                                                                                                             | Reason/detail for inclusion                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-------------------|--------------------|------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| AWARD-9           | NCT02152371        | Pozzilli et al., 2017  | Placebo-controlled, randomized trial of the addition of once-weekly glucagon-like peptide-1 receptor agonist dulaglutide to titrated daily insulin glargine in patients with type 2 diabetes (AWARD-9)            | Patients were randomized to receive QW dulaglutide 1.50 mg or placebo with IG. Insulin dose assessments occurred QW, and insulin doses were adjusted to prevent the occurrence of hypoglycaemia or severe hyperglycaemia. The IG dose remained unchanged if baseline HbA1c was >8.0%; the IG dose was decreased by 20% if HbA1c was ≤8.0% immediately after randomization to avoid hypoglycaemia in patients receiving dulaglutide.                                                                                                                                                                                                                                                                                                                                                                          |
| Buse et al., 2011 | NCT00765817        | Buse et al., 2011      | Use of twice-daily exenatide in basal insulin-treated patients with type 2 diabetes: a randomized, controlled trial                                                                                               | Participants continued their prestudy doses of oral antihyperglycaemic agents and were randomized to receive exenatide (5 µg BID for 4 wk and 10 µg BID thereafter) or placebo injections. At randomization, participants with HbA1c >8.0% continued to receive their current IG dose; those with HbA1c ≤8.0% had their dose decreased by 20%.                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| DURATION-7        | NCT02229383        | Guja et al., 2018      | Effect of exenatide QW or placebo, both added to titrated insulin glargine, in uncontrolled type 2 diabetes: the DURATION-7 randomized study                                                                      | Patients were randomized to receive QW exenatide 2 mg or placebo injection in addition to their existing IG ± metformin regimen. A stable dose of metformin was continued throughout the study. From wk 12, patients with inadequate glycaemic control received open-label rescue treatment with prandial insulin if FPG was >270, >240, or >200 mg/dL (>15, >13.3, or >11.1 mmol/L) during wk 12–18, 18–24, or 24–28, respectively.                                                                                                                                                                                                                                                                                                                                                                         |
| GetGoal-Duo 1     | NCT00975286        | Riddle et al., 2013(a) | Adding once-daily lixisenatide for type 2 diabetes inadequately controlled with newly initiated and continuously titrated basal insulin glargine: a 24-week, randomized, placebo-controlled study (GetGoal-Duo 1) | IG was added and systematically titrated during a 12-wk run-in, after which candidates with fasting glucose ≤7.8 mmol/L and HbA1c 7%–9% were randomized to lixisenatide 20 µg or placebo. A 2-step dosage increase was used with both placebo and lixisenatide (10 µg for 1 wk, 15 µg for 1 wk, and then 20-µg maintenance dosage if tolerated), with injections self-administered by participants ≤1 h before breakfast.                                                                                                                                                                                                                                                                                                                                                                                    |
| GetGoal-L         | NCT00715624        | Riddle et al., 2013(b) | Adding once-daily lixisenatide for type 2 diabetes inadequately controlled by established basal insulin: a 24-week, randomized, placebo-controlled comparison (GetGoal-L)                                         | Patients were randomized to QD lixisenatide or placebo in a 2-step dose-increase regimen (10 µg for 1 wk, 15 µg for 1 wk, and then 20 µg if tolerated) given subcutaneously within 1 h before the morning meal. Metformin was continued at a stable dose throughout the study. The basal insulin dosage was to remain relatively stable (±20%) throughout the study. After wk 12, no further dose adjustments of basal insulin were to be made except for reductions in response to hypoglycaemia.                                                                                                                                                                                                                                                                                                           |
| SURPASS-5         | NCT04039503        | Dahl et al., 2022      | Effect of subcutaneous tirzepatide vs placebo added to titrated insulin glargine on glycemic control in patients with type 2 diabetes: the SURPASS-5 randomized clinical trial                                    | Patients were randomized to receive QW tirzepatide 5, 10, or 15 mg or volume-matched placebo; initial 4-wk insulin stabilization period followed by a 36-wk insulin titration period; IG (100 U/mL) QD was continued for the treatment period. Patients with HbA1c ≤8.0% at randomization had their dose of IG reduced by 20% to reduce the potential risk of hypoglycaemia. All patients started tirzepatide at a 2.5-mg dose, which was increased by 2.5 mg every 4 wk until the randomly assigned dose was achieved. Patients in the comparator group received matching doses of placebo. Patients using metformin at baseline were to continue using the same dose and formulation. Overall, the intent was to include studies with roughly similar types of doses and dose titrations during the study. |

*BID* Twice daily, *FPG* Fasting plasma glucose, *GIP* Glucose-dependent insulinotropic polypeptide, *GLP-1* Glucagon-like peptide-1, *h* Hour(s), *HbA1c* Glycated haemoglobin, *IG* Insulin glargine, *QD* Once daily, *QW* Once weekly, *wk* Week(s).

**Table S2.2** Summary of trials identified in the systematic literature review and rationale for their exclusion from the network meta-analysis ( $n = 199$ )

| Study ID                                                                                                                  | Clinical trial No. | Author, year                     | Title                                                                                                                                                                                                                                      | Reason/detail for exclusion                                |
|---------------------------------------------------------------------------------------------------------------------------|--------------------|----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|
| <b>Patients not treated with basal insulin therapy <math>\pm</math> OADs as background therapy (<math>n = 196</math>)</b> |                    |                                  |                                                                                                                                                                                                                                            |                                                            |
| AWARD-7                                                                                                                   | NCT01621178        | Lilly CSR<br>Tuttle et al., 2018 | GBDX CSR<br>Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial                                                      | Renal study                                                |
| Hiramatsu et al., 2018                                                                                                    | NR                 | Hiramatsu et al., 2018           | Liraglutide relieves cardiac dilated function than DPP-4 inhibitors                                                                                                                                                                        | Renal study                                                |
| LIRA-RENAL                                                                                                                | NCT01620489        | Davies et al., 2016              | Efficacy and safety of liraglutide versus placebo as add-on to glucose-lowering therapy in patients with type 2 diabetes and moderate renal impairment (LIRA-RENAL): a randomized clinical trial                                           | Renal study                                                |
| PIONEER 5                                                                                                                 | NCT02827708        | Mosenzon et al., 2019            | Efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment (PIONEER 5): a placebo-controlled, randomised, phase 3a trial                                                                       | Renal study                                                |
| Wang et al. 2020(a)                                                                                                       | NCT02690883        | Wang et al., 2020(a)             | Exenatide and renal outcomes in patients with type 2 diabetes and diabetic kidney disease: a multicenter, randomized, parallel study                                                                                                       | Renal study                                                |
| Distiller et al., 2014                                                                                                    | NR                 | Distiller et al., 2014           | A 24-week, prospective, randomized, open-label, treat-to-target pilot study of obese type 2 diabetes patients with severe insulin resistance to assess the addition of exenatide on the efficacy of U-500 regular insulin plus metformin   | Study conducted in patients with severe insulin resistance |
| ELIXA                                                                                                                     | NCT01147250        | Pfeffer et al., 2015             | Lixisenatide in patients with type 2 diabetes and acute coronary syndrome                                                                                                                                                                  | CVOT                                                       |
| EXSCEL                                                                                                                    | NCT01144338        | Holman et al., 2017              | Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes                                                                                                                                                             | CVOT                                                       |
| HARMONY OUTCOMES                                                                                                          | NCT02465515        | Hernandez et al., 2018           | Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial                                                                | CVOT                                                       |
| LEADER                                                                                                                    | NCT01179048        | Marso et al., 2016               | Liraglutide and cardiovascular outcomes in type 2 diabetes                                                                                                                                                                                 | CVOT                                                       |
| PIONEER 6                                                                                                                 | NCT02692716        | Husain et al., 2019              | Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes                                                                                                                                                              | CVOT                                                       |
| REWIND                                                                                                                    | NCT01394952        | Gerstein et al., 2019            | Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial                                                                                                                   | CVOT                                                       |
| SUSTAIN-6                                                                                                                 | NCT01720446        | Marso et al., 2016(a)            | Semaglutide and cardiovascular outcomes in patients with type 2 diabetes                                                                                                                                                                   | CVOT                                                       |
| GetGoal-L-Asia                                                                                                            | NCT00866658        | Seino et al., 2012               | Randomized, double-blind, placebo-controlled trial of the once-daily GLP-1 receptor agonist lixisenatide in Asian patients with type 2 diabetes insufficiently controlled on basal insulin with or without a sulfonylurea (GetGoal-L-Asia) | Study conducted mainly in the Asian population             |
| GetGoal-L-C                                                                                                               | NCT01632163        | Yang et al., 2018                | Efficacy and safety of lixisenatide in a predominantly Asian population with type 2 diabetes insufficiently controlled with basal insulin: the GetGoal-L-C randomized trial                                                                | Study conducted mainly in the Asian population             |
| Jiang et al., 2021                                                                                                        | NR                 | Jiang et al., 2021               | Comparison of dapagliflozin and liraglutide in patients with poorly controlled type 2 diabetes mellitus: a 24-week, open, double-centered, head to head trial                                                                              | Study conducted mainly in the Asian population             |
| LIRA-Ramadan                                                                                                              | NCT01917656        | Azar et al., 2016                | Efficacy and safety of liraglutide compared to sulphonylurea during Ramadan in patients with type 2 diabetes (LIRA-Ramadan): a randomized trial                                                                                            | Study conducted during Ramadan                             |
| AWARD-3                                                                                                                   | NCT01126580        | Lilly CSR                        | GBDC CSR                                                                                                                                                                                                                                   | Study with no background therapy                           |

| Study ID                | Clinical trial No.  | Author, year               | Title                                                                                                                                                                                                                                               | Reason/detail for exclusion                                                                                                                                                                                                                                               |
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|                         |                     | Umpierrez et al., 2014     | Efficacy and safety of dulaglutide monotherapy versus metformin in type 2 diabetes in a randomized controlled trial (AWARD-3)                                                                                                                       |                                                                                                                                                                                                                                                                           |
| Chen et al., 2018       | NCT01644500         | Chen et al., 2018          | Efficacy and safety of dulaglutide monotherapy compared with glimepiride in East-Asian patients with type 2 diabetes in a multicentre, double-blind, randomized, parallel-arm, active comparator, phase III trial                                   | Study with no background therapy                                                                                                                                                                                                                                          |
| CONFIDENCE              | NCT01147627         | Xu et al., 2015(a)         | Comparison of the effects on glycaemic control and $\beta$ -cell function in newly diagnosed type 2 diabetes patients of treatment with exenatide, insulin or pioglitazone: a multicentre randomized parallel-group trial (the CONFIDENCE study)    | Study with no background therapy                                                                                                                                                                                                                                          |
| DURATION-4              | NCT00676338         | Russell-Jones et al., 2012 | Efficacy and safety of exenatide once weekly versus metformin, pioglitazone, and sitagliptin used as monotherapy in drug-naïve patients with type 2 diabetes (DURATION-4): a 26-week double-blind study                                             | Study with no background therapy                                                                                                                                                                                                                                          |
| Feng et al., 2019       | NCT03068065         | Feng et al., 2019          | Effects of liraglutide, metformin and glimepiride on body composition in patients with both type 2 diabetes and non-alcoholic fatty liver disease: a randomized trial                                                                               | Study with no background therapy                                                                                                                                                                                                                                          |
| Lambadiari et al., 2018 | NCT03010683         | Lambadiari et al., 2018    | Effects of 6-month treatment with the glucagon like peptide-1 analogue liraglutide on arterial stiffness, left ventricular myocardial deformation and oxidative stress in subjects with newly diagnosed type 2 diabetes                             | Study with no background therapy                                                                                                                                                                                                                                          |
| LEAD-3                  | NCT00294723         | Garber et al., 2009        | Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial                                                                                              | Study with no background therapy                                                                                                                                                                                                                                          |
|                         |                     | Garber et al., 2011        | Liraglutide, a once-daily human glucagon-like peptide 1 analogue, provides sustained improvements in glycaemic control and weight for 2 years as monotherapy compared with glimepiride in patients with type 2 diabetes                             |                                                                                                                                                                                                                                                                           |
| Li et al., 2015         | NR                  | Li et al., 2015            | Effect of exenatide, insulin and pioglitazone on bone metabolism in patients with newly diagnosed type 2 diabetes                                                                                                                                   | Study with no background therapy                                                                                                                                                                                                                                          |
| Liu et al., 2017        | ChiCTR-IPR-16008578 | Liu et al., 2017           | Liraglutide and metformin alone or combined therapy for type 2 diabetes patients complicated with coronary artery disease                                                                                                                           | Study with no background therapy                                                                                                                                                                                                                                          |
| Liu et al., 2020        | NCT02303730         | Liu et al., 2020           | Efficacy of exenatide and insulin glargine on nonalcoholic fatty liver disease in patients with type 2 diabetes                                                                                                                                     | Study with no background therapy                                                                                                                                                                                                                                          |
| Miyagawa et al., 2015   | NCT01558271         | Miyagawa et al., 2015      | Once-weekly glucagon-like peptide-1 receptor agonist dulaglutide is non-inferior to once-daily liraglutide and superior to placebo in Japanese patients with type 2 diabetes: a 26-week randomized phase III study                                  | Study with no background therapy                                                                                                                                                                                                                                          |
|                         |                     | Odawara et al., 2016       | Once-weekly glucagon-like peptide-1 receptor agonist dulaglutide significantly decreases glycated haemoglobin compared with once-daily liraglutide in Japanese patients with type 2 diabetes: 52 weeks of treatment in a randomized phase III study |                                                                                                                                                                                                                                                                           |
| Moretto et al., 2008    | NCT00381342         | Moretto et al., 2008       | Efficacy and tolerability of exenatide monotherapy over 24 weeks in antidiabetic drug-naïve patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, parallel-group study                                                     | Study with no background therapy                                                                                                                                                                                                                                          |
| SURPASS J-mono          | NCT03861052         | Lilly CSR                  | GPGO CSR                                                                                                                                                                                                                                            | Study with no background therapy; Inagaki N, Takeuchi M, Oura T, Imaoka T, Seino Y. Efficacy and safety of tirzepatide monotherapy compared with dulaglutide in Japanese patients with type 2 diabetes (SURPASS J-mono): a double-blind, multicentre, randomised, phase 3 |

| Study ID              | Clinical trial No. | Author, year            | Title                                                                                                                                                                                                                                                                                  | Reason/detail for exclusion                                                                                                                                                                                                                                                                                                                                                                                                                          |
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|                       |                    |                         |                                                                                                                                                                                                                                                                                        | trial. Lancet Diabetes Endocrinol. 2022;10(9):623–33.                                                                                                                                                                                                                                                                                                                                                                                                |
| SURPASS-1             | NCT03954834        | Rosenstock et al., 2021 | Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial                                                                                                                 | Study with no background therapy                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                       |                    | Lilly CSR GPGK          | GPGK CSR                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Yamamoto et al., 2018 | UMIN000028313      | Yamamoto et al., 2018   | Comparison of liraglutide plus basal insulin and basal-bolus insulin therapy (BBIT) for glycemic control, body weight stability, and treatment satisfaction in patients treated using BBIT for type 2 diabetes without severe insulin deficiency: a randomized prospective pilot study | Study with no background therapy                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Yuan et al., 2012     | NR                 | Yuan et al., 2012       | Efficacy and tolerability of exenatide monotherapy in obese patients with newly diagnosed type 2 diabetes: a randomized, 26 weeks metformin-controlled, parallel-group study                                                                                                           | Study with no background therapy                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Zhang et al., 2020(b) | NR                 | Zhang et al., 2020(b)   | Effect of liraglutide therapy on serum fetuin A in patients with type 2 diabetes and non-alcoholic fatty liver disease                                                                                                                                                                 | Study with no background therapy                                                                                                                                                                                                                                                                                                                                                                                                                     |
| PIONEER 1             | NCT02906930        | Aroda et al., 2019(a)   | PIONEER 1: Randomized clinical trial of the efficacy and safety of oral semaglutide monotherapy in comparison with placebo in patients with type 2 diabetes                                                                                                                            | Study with no background therapy.<br><b>Details:</b> All patients randomized to oral semaglutide initiated treatment with 3 mg QD with dose escalations every 4 wk until the randomized maintenance dose was achieved. There was no background therapy, so the trial was not comparable to SURPASS-5. Oral semaglutide was given as first-line monotherapy, while metformin is usually recommended as first-line pharmacotherapy in T2DM management. |
| PIONEER 9             | NCT03018028        | Yamada et al., 2020     | Dose-response, efficacy, and safety of oral semaglutide monotherapy in Japanese patients with type 2 diabetes (PIONEER 9): a 52-week, phase 2/3a, randomised, controlled trial                                                                                                         | Study with no background therapy.<br><b>Details:</b> Patients treated for ≥30 d before screening with oral glucose-lowering drug monotherapy at a stable daily dose for uncontrolled T2DM managed by diet or exercise or with oral glucose-lowering drug monotherapy (washed out) were randomly assigned to receive double-blind QD oral semaglutide (3, 7, or 14 mg) or placebo, or open-label s.c. QD liraglutide 0.9 mg.                          |
| Seino et al., 2018    | NCT02254291        | Seino et al., 2018      | Safety and efficacy of semaglutide once weekly vs sitagliptin once daily, both as monotherapy in Japanese people with type 2 diabetes                                                                                                                                                  | Study with no background therapy.<br><b>Details:</b> Treated with either diet and exercise therapy in addition to OAD monotherapy if HbA1c was 6.5%–9.5% (48–80 mmol/mol) or with diet and exercise therapy only if HbA1c was 7.0%–10.5% (53–91 mmol/mol) for ≥30 d before screening.                                                                                                                                                                |
| SUSTAIN 1             | NCT02054897        | Sorli et al., 2017      | Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial                                                      | Study with no background therapy.<br><b>Details:</b> Treated with diet and exercise alone for ≥30 d; no background therapy.                                                                                                                                                                                                                                                                                                                          |
| LIRA-ADD2BASAL        | NCT01617434        | Ahmann et al., 2015     | Efficacy and safety of liraglutide versus placebo added to basal insulin analogues (with or without metformin) in patients with type 2 diabetes: a randomized, placebo-controlled trial                                                                                                | Study with no insulin titration.<br><b>Details:</b> Subjects were randomized 1:1 to receive QD liraglutide 1.8 mg or placebo. Liraglutide or                                                                                                                                                                                                                                                                                                         |

| Study ID                | Clinical trial No.  | Author, year            | Title                                                                                                                                                                                                                                                             | Reason/detail for exclusion                                                                                                                                                                                                                                                                                                                                                                                                   |
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|                         |                     |                         |                                                                                                                                                                                                                                                                   | placebo was initiated at 0.6 mg/d, increased in weekly increments of 0.6 mg to a final dose of 1.8 mg/d, which was then continued for the remainder of the study. The study medication (liraglutide or placebo) was added to the subject's stable prestudy basal insulin analog regimen $\pm$ metformin. However, capping the basal insulin analog dose at a level equal to the prestudy level was a limitation of the study. |
| PIONEER 7               | NCT02849080         | Pieber et al., 2019     | Efficacy and safety of oral semaglutide with flexible dose adjustment versus sitagliptin in type 2 diabetes (PIONEER 7): a multicentre, open-label, randomised, phase 3a trial                                                                                    | Flexible dose study with no further comparator of interest.<br><b>Details:</b> Receiving stable daily doses of 1 or 2 glucose-lowering drugs (metformin, SU, SGLT2 inhibitors, or thiazolidinediones) for $\geq 90$ d before screening; oral semaglutide QD with flexible dose adjustment or oral sitagliptin 100 mg QD, in addition to existing background glucose-lowering medication. No placebo comparator.               |
| Charbonnel et al., 2013 | NCT01296412         | Charbonnel et al., 2013 | Efficacy and safety over 26 weeks of an oral treatment strategy including sitagliptin compared with an injectable treatment strategy with liraglutide in patients with type 2 diabetes mellitus inadequately controlled on metformin: a randomised clinical trial | Flexible dose study with no further comparator of interest                                                                                                                                                                                                                                                                                                                                                                    |
| Yang et al., 2020       | ChiCTR-IPR-15006558 | Yang et al., 2020       | Efficacy and safety of generic exenatide injection in Chinese patients with type 2 diabetes: a multicenter, randomized, controlled, non-inferiority trial                                                                                                         | Flexible dose study with no further comparator of interest                                                                                                                                                                                                                                                                                                                                                                    |
| 1860-LIRA-DPP-4         | NCT00700817         | Pratley et al., 2010    | Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial                                                                              | Study of patients with 1 to 2 OADs                                                                                                                                                                                                                                                                                                                                                                                            |
|                         |                     | Pratley et al., 2011    | One year of liraglutide treatment offers sustained and more effective glycaemic control and weight reduction compared with sitagliptin, both in combination with metformin, in patients with type 2 diabetes: a randomised, parallel-group, open-label trial      |                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                         |                     | Pratley et al., 2012    | Efficacy and safety of switching from the DPP-4 inhibitor sitagliptin to the human GLP-1 analog liraglutide after 52 weeks in metformin-treated patients with type 2 diabetes a randomized, open-label trial                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Apovian et al., 2010    | NR                  | Apovian et al., 2010    | Effects of exenatide combined with lifestyle modification in patients with type 2 diabetes                                                                                                                                                                        | Study of patients with 1 to 2 OADs                                                                                                                                                                                                                                                                                                                                                                                            |
| Araki et al., 2015      | NCT01584232         | Araki et al., 2015      | Efficacy and safety of once-weekly dulaglutide in combination with sulphonylurea and/or biguanide compared with once-daily insulin glargine in Japanese patients with type 2 diabetes: a randomized, open-label, phase III, non-inferiority study                 | Study of patients with 1 to 2 OADs                                                                                                                                                                                                                                                                                                                                                                                            |
| AWARD-1                 | NCT01064687         | Lilly CSR               | GBDA CSR                                                                                                                                                                                                                                                          | Study of patients with 1 to 2 OADs                                                                                                                                                                                                                                                                                                                                                                                            |
|                         |                     | Wysham et al., 2014(a)  | Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1)                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                               |
| AWARD-10                | NCT02597049         | Lilly CSR               | GBGE CSR                                                                                                                                                                                                                                                          | Study of patients with 1 to 2 OADs                                                                                                                                                                                                                                                                                                                                                                                            |

| Study ID                       | Clinical trial No. | Author, year                    | Title                                                                                                                                                                                                                               | Reason/detail for exclusion        |
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| AWARD-11                       | NCT03495102        | Ludvik et al., 2018             | Dulaglutide as add-on therapy to SGLT2 inhibitors in patients with inadequately controlled type 2 diabetes (AWARD-10): a 24-week, randomised, double-blind, placebo-controlled trial                                                | Study of patients with 1 to 2 OADs |
|                                |                    | Lilly CSR<br>Frias et al., 2021 | GBGL CSR<br>Efficacy and safety of dulaglutide 3.0 mg and 4.5 mg versus dulaglutide 1.50 mg in metformin-treated patients with type 2 diabetes in a randomized controlled trial (AWARD-11)                                          |                                    |
| AWARD-2                        | NCT01075282        | Lilly CSR                       | GBDB CSR                                                                                                                                                                                                                            | Study of patients with 1 to 2 OADs |
|                                |                    | Giorgino et al., 2015           | Efficacy and safety of once-weekly dulaglutide versus insulin glargine in patients with type 2 diabetes on metformin and glimepiride (AWARD-2)                                                                                      |                                    |
| AWARD-5                        | NCT00734474        | Lilly CSR                       | GBCF CSR                                                                                                                                                                                                                            | Study of patients with 1 to 2 OADs |
|                                |                    | Nauck et al., 2014              | Efficacy and safety of dulaglutide versus sitagliptin after 52 weeks in type 2 diabetes in a randomized controlled trial (AWARD-5)                                                                                                  |                                    |
|                                |                    | Skrivanek et al., 2014          | Dose-finding results in an adaptive, seamless, randomized trial of once-weekly dulaglutide combined with metformin in type 2 diabetes patients (AWARD-5)                                                                            |                                    |
|                                |                    | Weinstock et al., 2015          | Safety and efficacy of once-weekly dulaglutide versus sitagliptin after 2 years in metformin-treated patients with type 2 diabetes (AWARD-5): a randomized, phase III study                                                         |                                    |
| AWARD-6                        | NCT01624259        | Lilly CSR                       | GBDE CSR                                                                                                                                                                                                                            | Study of patients with 1 to 2 OADs |
|                                |                    | Dungan et al., 2014             | Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial                                                        |                                    |
| Bergenstal et al., 2009        | NCT00097877        | Bergenstal et al., 2009         | Efficacy and safety of biphasic insulin aspart 70/30 versus exenatide in subjects with type 2 diabetes failing to achieve glycemic control with metformin and a sulfonylurea                                                        | Study of patients with 1 to 2 OADs |
| Bunck et al., 2009/2010/2011   | NCT00097500        | Bunck et al., 2009              | One-year treatment with exenatide improves beta-cell function, compared with insulin glargine, in metformin-treated type 2 diabetic patients: a randomized, controlled trial                                                        | Study of patients with 1 to 2 OADs |
|                                |                    | Bunck et al., 2010 (a)          | Exenatide affects circulating cardiovascular risk biomarkers independently of changes in body composition                                                                                                                           |                                    |
|                                |                    | Bunck et al., 2010 (b)          | One-year treatment with exenatide vs. insulin glargine: effects on postprandial glycemia, lipid profiles, and oxidative stress                                                                                                      |                                    |
|                                |                    | Bunck et al., 2011              | Exenatide treatment did not affect bone mineral density despite body weight reduction in patients with type 2 diabetes                                                                                                              |                                    |
| Davies et al., 2013            | NCT01003184        | Davies et al., 2013             | Once-weekly exenatide versus once- or twice-daily insulin detemir: randomized, open-label, clinical trial of efficacy and safety in patients with type 2 diabetes treated with metformin alone or in combination with sulfonylureas | Study of patients with 1 to 2 OADs |
| DeFronzo et al., 2005          | NR                 | DeFronzo et al., 2005           | Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes                                                                                                    | Study of patients with 1 to 2 OADs |
| Derosa et al., 2010            | NR                 | Derosa et al., 2010             | Exenatide versus glibenclamide in patients with diabetes                                                                                                                                                                            | Study of patients with 1 to 2 OADs |
| Derosa et al., 2011            | NR                 | Derosa et al., 2011             | Exenatide or glimepiride added to metformin on metabolic control and on insulin resistance in type 2 diabetic patients                                                                                                              | Study of patients with 1 to 2 OADs |
| Derosa et al., 2012/2013(a, b) | NR                 | Derosa et al., 2012             | Exenatide plus metformin compared with metformin alone on $\beta$ -cell function in patients with type 2 diabetes                                                                                                                   | Study of patients with 1 to 2 OADs |

| Study ID               | Clinical trial No. | Author, year            | Title                                                                                                                                                                                                                                                                    | Reason/detail for exclusion        |
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|                        |                    | Derosa et al., 2013(c)  | Effects of exenatide and metformin in combination on some adipocytokine levels: a comparison with metformin monotherapy                                                                                                                                                  |                                    |
|                        |                    | Derosa et al., 2013(d)  | Variation in inflammatory markers and glycemic parameters after 12 months of exenatide plus metformin treatment compared with metformin alone: a randomized placebo-controlled trial                                                                                     |                                    |
| DUAL I                 | NCT01336023        | Gough et al., 2014      | Efficacy and safety of a fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with its components given alone: results of a phase 3, open-label, randomised, 26-week, treat-to-target trial in insulin-naïve patients with type 2 diabetes    | Study of patients with 1 to 2 OADs |
|                        |                    | Gough et al., 2015      | One-year efficacy and safety of a fixed combination of insulin degludec and liraglutide in patients with type 2 diabetes: results of a 26-week extension to a 26-week main trial                                                                                         |                                    |
| DURATION-2             | NCT00637273        | Bergenstal et al., 2010 | Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial                                                                                             | Study of patients with 1 to 2 OADs |
| DURATION-3             | NCT00641056        | Diamant et al., 2010    | Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial                                                                                                                    | Study of patients with 1 to 1 OADs |
|                        |                    | Diamant et al., 2012    | Safety and efficacy of once-weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes over 84 weeks                                                                                                                            |                                    |
|                        |                    | Diamant et al., 2014    | Exenatide once weekly versus insulin glargine for type 2 diabetes (DURATION-3): 3-year results of an open-label randomised trial                                                                                                                                         |                                    |
| DURATION-6             | NCT01029886        | Buse et al., 2013       | Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study                                                                                                                                        | Study of patients with 1 to 2 OADs |
| DURATION-8             | NCT02229396        | Frias et al., 2016      | Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial | Study of patients with 1 to 2 OADs |
|                        |                    | Jabbour et al., 2018    | Safety and efficacy of exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy: 52-week results of the DURATION-8 randomized controlled trial    |                                    |
|                        |                    | Jabbour et al., 2020    | Efficacy and safety over 2 years of exenatide plus dapagliflozin in the DURATION-8 study: a multicenter, double-blind, phase 3, randomized controlled trial                                                                                                              |                                    |
| EAGLE                  | NR                 | D'Alessio et al., 2015  | Comparison of insulin glargine and liraglutide added to oral agents in patients with poorly controlled type 2 diabetes                                                                                                                                                   | Study of patients with 1 to 2 OADs |
| EUREXA                 | NCT00359762        | Gallwitz et al., 2012   | Exenatide twice daily versus glimepiride for prevention of glycaemic deterioration in patients with type 2 diabetes with metformin failure (EUREXA): an open-label, randomised controlled trial                                                                          | Study of patients with 1 to 2 OADs |
|                        |                    | Simó et al., 2015       | Long-term changes in cardiovascular risk markers during administration of exenatide twice daily or glimepiride: results from the European exenatide study                                                                                                                |                                    |
| Ferdinand et al., 2014 | NCT01149421        | Ferdinand et al., 2014  | Effects of the once-weekly glucagon-like peptide-1 receptor agonist dulaglutide on ambulatory blood pressure and heart rate in patients with type 2 diabetes mellitus                                                                                                    | Study of patients with 1 to 2 OADs |

| Study ID              | Clinical trial No. | Author, year            | Title                                                                                                                                                                                                                                                                     | Reason/detail for exclusion        |
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| Frias et al., 2018    | NCT03131687        | Frias et al., 2018      | Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial                                                                          | Study of patients with 1 to 2 OADs |
| Gallwitz et al., 2011 | NCT00434954        | Gallwitz et al., 2011   | Exenatide twice daily versus premixed insulin aspart 70/30 in metformin-treated patients with type 2 diabetes: a randomized 26-week study on glycemic control and hypoglycemia                                                                                            | Study of patients with 1 to 2 OADs |
| GetGoal-F1            | NCT00763451        | Bolli et al., 2014      | Efficacy and safety of lixisenatide once daily vs. placebo in people with type 2 diabetes insufficiently controlled on metformin (GetGoal-F1)                                                                                                                             | Study of patients with 1 to 2 OADs |
| GetGoal-M             | NCT00712673        | Ahrén et al., 2013      | Efficacy and safety of lixisenatide once-daily morning or evening injections in type 2 diabetes inadequately controlled on metformin (GetGoal-M)                                                                                                                          | Study of patients with 1 to 2 OADs |
| GetGoal-M-Asia        | NCT01169779        | Yu Pan et al., 2014     | Lixisenatide treatment improves glycaemic control in Asian patients with type 2 diabetes mellitus inadequately controlled on metformin with or without sulfonylurea: a randomized, double-blind, placebo-controlled, 24-week trial (GetGoal-M-Asia)                       | Study of patients with 1 to 2 OADs |
| GetGoal-P             | NCT00763815        | Pinget et al., 2013     | Efficacy and safety of lixisenatide once daily versus placebo in type 2 diabetes insufficiently controlled on pioglitazone (GetGoal-P)                                                                                                                                    | Study of patients with 1 to 2 OADs |
| GetGoal-S             | NCT00713830        | Rosenstock et al., 2014 | Beneficial effects of once-daily lixisenatide on overall and postprandial glycemic levels without significant excess of hypoglycemia in type 2 diabetes inadequately controlled on a sulfonylurea with or without metformin (GetGoal-S)                                   | Study of patients with 1 to 2 OADs |
| GetGoal-X             | NCT00707031        | Rosenstock et al., 2013 | Efficacy and safety of lixisenatide once daily versus exenatide twice daily in type 2 diabetes inadequately controlled on metformin: a 24-week, randomized, open-label, active-controlled study (GetGoal-X)                                                               | Study of patients with 1 to 2 OADs |
| Guo et al., 2020      | ChiCTR2000035091   | Guo et al., 2020        | Liraglutide or insulin glargine treatments improves hepatic fat in obese patients with type 2 diabetes and nonalcoholic fatty liver disease in twenty-six weeks: a randomized placebo-controlled trial                                                                    | Study of patients with 1 to 2 OADs |
| Gurkan et al., 2014   | NR                 | Gürkan et al., 2014     | Evaluation of exenatide versus insulin glargine for the impact on endothelial functions and cardiovascular risk markers                                                                                                                                                   | Study of patients with 1 to 2 OADs |
|                       |                    | Gürkan et al., 2017     | Effect of exenatide on aortic stiffness and blood pressure parameters                                                                                                                                                                                                     |                                    |
| GWAA                  | NCT00082381        | Heine et al., 2005      | Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial                                                                                                                                                            | Study of patients with 1 to 2 OADs |
| HARMONY 7             | NCT01128894        | Pratley et al., 2014    | Once-weekly albiglutide versus once-daily liraglutide in patients with type 2 diabetes inadequately controlled on oral drugs (HARMONY 7): a randomised, open-label, multicentre, non-inferiority phase 3 study                                                            | Study of patients with 1 to 2 OADs |
| HEELA                 | NR                 | Davies et al., 2009     | Exenatide compared with long-acting insulin to achieve glycaemic control with minimal weight gain in patients with type 2 diabetes: results of the Helping Evaluate Exenatide in patients with diabetes compared with Long-Acting insulin (HEELA) study                   | Study of patients with 1 to 2 OADs |
| Inagaki et al., 2012  | NCT00935532        | Inagaki et al., 2012    | Efficacy and safety profile of exenatide once weekly compared with insulin once daily in Japanese patients with type 2 diabetes treated with oral antidiabetes drug(s): results from a 26-week, randomized, open-Label, parallel-group, multicenter, noninferiority study | Study of patients with 1 to 2 OADs |
| Ji et al., 2013       | NCT00917267        | Ji et al., 2013         | Efficacy and safety of exenatide once-weekly vs exenatide twice-daily in Asian patients with type 2 diabetes mellitus                                                                                                                                                     | Study of patients with 1 to 2 OADs |

| Study ID              | Clinical trial No. | Author, year               | Title                                                                                                                                                                                                                                              | Reason/detail for exclusion        |
|-----------------------|--------------------|----------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|
| Kadowaki et al., 2011 | NCT00577824        | Kadowaki et al., 2011      | Improved glycemic control and reduced bodyweight with exenatide: a double-blind, randomized, phase 3 study in Japanese patients with suboptimally controlled type 2 diabetes over 24 weeks                                                         | Study of patients with 1 to 2 OADs |
|                       |                    | Inagaki et al., 2011       | Long-term safety and efficacy of exenatide twice daily in Japanese patients with suboptimally controlled type 2 diabetes                                                                                                                           |                                    |
| Kendall et al., 2005  | NR                 | Kendall et al., 2005       | Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea                                                                                                      | Study of patients with 1 to 2 OADs |
| LEAD-2                | NCT00318461        | Nauck et al., 2009         | Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study                                                       | Study of patients with 1 to 2 OADs |
|                       |                    | Nauck et al., 2013         | Long-term efficacy and safety comparison of liraglutide, glimepiride and placebo, all in combination with metformin in type 2 diabetes: 2-year results from the LEAD-2 study                                                                       |                                    |
| LEAD-4                | NCT00333151        | Zinman et al., 2009        | Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD)                                                                  | Study of patients with 1 to 2 OADs |
| LEAD-5                | NCT00331851        | Russell-Jones et al., 2009 | Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial                                                                      | Study of patients with 1 to 2 OADs |
| LEAD-6                | NCT00518882        | Buse et al., 2009          | Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6)                                                                                            | Study of patients with 1 to 2 OADs |
| Li et al., 2014       | NR                 | Li et al., 2014            | Efficacy and safety comparison of add-on therapy with liraglutide, saxagliptin and vildagliptin, all in combination with current conventional oral hypoglycemic agents therapy in poorly controlled Chinese type 2 diabetes                        | Study of patients with 1 to 2 OADs |
| Light-On              | NCT02147925        | Yan et al., 2019           | Liraglutide, sitagliptin, and insulin glargine added to metformin: the effect on body weight and intrahepatic lipid in patients with type 2 diabetes mellitus and nonalcoholic fatty liver disease                                                 | Study of patients with 1 to 2 OADs |
| LIRA-ADD2SGLT2i       | NCT02964247        | Blonde et al., 2021        | Liraglutide as add-on to sodium-glucose co-transporter-2 inhibitors in patients with inadequately controlled type 2 diabetes: LIRA-ADD2SGLT2i, a 26-week, randomized, double-blind, placebo-controlled trial                                       | Study of patients with 1 to 2 OADs |
| LIRA-SWITCH           | NCT01907854        | Bailey et al., 2016        | Efficacy and safety of switching from sitagliptin to liraglutide in subjects with type 2 diabetes (LIRA-SWITCH): a randomized, double-blind, double-dummy, active-controlled 26-week trial                                                         | Study of patients with 1 to 2 OADs |
| Liutkus et al., 2010  | NR                 | Liutkus et al., 2010       | A placebo-controlled trial of exenatide twice-daily added to thiazolidinediones alone or in combination with metformin                                                                                                                             | Study of patients with 1 to 2 OADs |
| LixiLan-O             | NCT02058147        | Rosenstock et al., 2016    | Benefits of LixiLan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide, versus insulin glargine and lixisenatide monocomponents in type 2 diabetes inadequately controlled on oral agents: the LixiLan-O randomized trial | Study of patients with 1 to 2 OADs |
| LYDIA                 | NCT02043054        | Webb et al., 2020          | A randomized, open-label, active comparator trial assessing the effects of 26 weeks of liraglutide or sitagliptin on cardiovascular function in young obese adults with type 2 diabetes                                                            | Study of patients with 1 to 2 OADs |
| Nauck et al., 2007    | NR                 | Nauck et al., 2007         | A comparison of twice-daily exenatide and biphasic insulin aspart in patients with type 2 diabetes who were suboptimally controlled with sulfonylurea and metformin: a non-inferiority study                                                       | Study of patients with 1 to 2 OADs |

| Study ID              | Clinical trial No. | Author, year                             | Title                                                                                                                                                                                                                                | Reason/detail for exclusion                                                                                                                                                                                                                                                                                                                                                                                                          |
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| Nauck et al., 2016    | NCT01973231        | Nauck et al., 2016                       | Once-daily liraglutide versus lixisenatide as add-on to metformin in type 2 diabetes: a 26-week randomized controlled clinical trial                                                                                                 | Study of patients with 1 to 2 OADs                                                                                                                                                                                                                                                                                                                                                                                                   |
| SURPASS-2             | NCT03987919        | Frias et al., 2021<br>Lilly CSR GPGL     | Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes<br>GPGL CSR                                                                                                                                              | Study of patients with 1 to 2 OADs                                                                                                                                                                                                                                                                                                                                                                                                   |
| SURPASS-3             | NCT03882970        | Ludvik et al., 2021<br>Lilly CSR GPGH    | Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial<br>GPGH CSR | Study of patients with 1 to 2 OADs                                                                                                                                                                                                                                                                                                                                                                                                   |
| SURPASS-4             | NCT03730662        | Del Prato et al., 2021<br>Lilly CSR GPGM | Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial<br>GPGM CSR                                               | Study of patients with 1 to 2 OADs                                                                                                                                                                                                                                                                                                                                                                                                   |
| Van Gaal et al., 2014 | NCT00976937        | Van Gaal et al., 2014                    | Efficacy and safety of the glucagon-like peptide-1 receptor agonist lixisenatide versus the dipeptidyl peptidase-4 inhibitor sitagliptin in young (<50 years) obese patients with type 2 diabetes mellitus                           | Study of patients with 1 to 2 OADs                                                                                                                                                                                                                                                                                                                                                                                                   |
| Wang et al., 2019     | NCT01648582        | Wang et al., 2019                        | Efficacy and safety of once-weekly dulaglutide versus insulin glargine in mainly Asian patients with type 2 diabetes mellitus on metformin and/or a sulphonylurea: a 52-week open-label, randomized phase III trial                  | Study of patients with 1 to 2 OADs                                                                                                                                                                                                                                                                                                                                                                                                   |
| Zang et al., 2016     | NCT02008682        | Zang et al., 2016                        | Efficacy and safety of liraglutide versus sitagliptin, both in combination with metformin, in Chinese patients with type 2 diabetes: a 26-week, open-label, randomized, active comparator clinical trial                             | Study of patients with 1 to 2 OADs                                                                                                                                                                                                                                                                                                                                                                                                   |
| PIONEER 2             | NCT02863328        | Rodbard et al., 2019                     | Oral semaglutide versus empagliflozin in patients with type 2 diabetes uncontrolled on metformin: the PIONEER 2 trial                                                                                                                | Study of patients with 1 to 2 OADs                                                                                                                                                                                                                                                                                                                                                                                                   |
| PIONEER 3             | NCT02607865        | Rosenstock et al., 2019                  | Effect of additional oral semaglutide vs sitagliptin on glycated hemoglobin in adults with type 2 diabetes uncontrolled with metformin alone or with sulfonylurea: the PIONEER 3 randomized clinical trial                           | Study of patients with 1 to 2 OADs.<br><b>Details:</b> Patients were randomized to receive QD oral semaglutide 3, 7, or 14 mg or sitagliptin (active comparator) 100 mg. Semaglutide was initiated at 3 mg/d and escalated every 4 wk, first to 7 mg/d then to 14 mg/d, until the randomized dosage was achieved. Patients also received background metformin with or without SU, maintained at the stable, pretrial dosage.         |
| PIONEER 4             | NCT02863419        | Pratley et al., 2019                     | Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial                                                                                              | Study of patients with 1 to 2 OADs.<br><b>Details:</b> Participants were randomly assigned to oral semaglutide, s.c. liraglutide, or placebo QD in addition to existing background glucose-lowering medication (metformin ± SGLT2 inhibitor).                                                                                                                                                                                        |
| SUSTAIN 10            | NCT03191396        | Capehorn et al., 2020                    | Efficacy and safety of once-weekly semaglutide 1.0mg vs once-daily liraglutide 1.2mg as add-on to 1-3 oral antidiabetic drugs in subjects with type 2 diabetes (SUSTAIN 10)                                                          | Study of patients with 1 to 2 OADs.<br><b>Details:</b> Subjects with T2DM inadequately controlled on 1–3 OADs were randomized to treatment with either s.c. QW semaglutide 1.0 mg or s.c. QD liraglutide 1.2 mg. After randomization, all subjects followed a dose-escalation regimen. The semaglutide maintenance dose was reached after an 8-wk escalation period consisting of 4 wk of 0.25 mg QW, followed by 4 wk of 0.5 mg QW. |

| Study ID      | Clinical trial No. | Author, year         | Title                                                                                                                                                                                                                                                                                     | Reason/detail for exclusion                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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|               |                    |                      |                                                                                                                                                                                                                                                                                           | The liraglutide maintenance dose was reached after 1 wk of 0.6 mg QD. The study had different dosing frequencies of semaglutide and liraglutide.                                                                                                                                                                                                                                                                                                                                            |
| SUSTAIN 2     | NCT01930188        | Ahrén et al., 2017   | Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial                                                    | Study of patients with 1 to 2 OADs                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| SUSTAIN 3     | NCT01885208        | Ahmann et al., 2018  | Efficacy and safety of once-weekly semaglutide versus exenatide ER in subjects with type 2 diabetes (SUSTAIN 3): a 56-week, open-label, randomized clinical trial                                                                                                                         | Study of patients with 1 to 2 OADs                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| SUSTAIN 4     | NCT02128932        | Aroda et al., 2017   | Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naïve patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial | Study of patients with 1 to 2 OADs.<br><b>Details:</b> Participants were randomly assigned to either s.c. QW 0.5 mg or 1.0 mg semaglutide (doses reached after following a fixed dose-escalation regimen) or QD insulin glargine (starting dose 10 IU/d, then titrated weekly to a prebreakfast self-measured plasma glucose target of 4.0–5.5 mmol/L [72–99 mg/dL]) for 30 wk. In all treatment groups, previous background metformin and SU treatment was continued throughout the trial. |
| SUSTAIN 7     | NCT02648204        | Pratley et al., 2018 | Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial                                                                                                                                                         | Study of patients with 1 to 2 OADs.<br><b>Details:</b> Eligible patients were on metformin monotherapy. Patients were randomly assigned to QW treatment with either semaglutide 0.5 mg, dulaglutide 0.75 mg, semaglutide 1.0 mg, or dulaglutide 1.50 mg s.c.                                                                                                                                                                                                                                |
| SUSTAIN 8     | NCT03136484        | Lingvay et al., 2019 | Efficacy and safety of once-weekly semaglutide versus daily canagliflozin as add-on to metformin in patients with type 2 diabetes (SUSTAIN 8): a double-blind, phase 3b, randomised controlled trial                                                                                      | Study of patients with 1 to 2 OADs                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| SUSTAIN 9     | NCT03086330        | Zinman et al., 2019  | Semaglutide once weekly as add-on to SGLT-2 inhibitor therapy in type 2 diabetes (SUSTAIN 9): a randomised, placebo-controlled trial                                                                                                                                                      | Study of patients with 1 to 2 OADs.<br><b>Details:</b> Adults were randomly assigned (1:1) to receive s.c. semaglutide 1.0 mg or volume-matched placebo QW for 30 wk, after a dose-escalation schedule of 4 wk of 0.25 mg semaglutide or placebo and 4 wk of 0.5 mg semaglutide or placebo. Existing antidiabetic medications, including SGLT2 inhibitor treatment, were continued for the duration of the trial.                                                                           |
| SUSTAIN China | NCT03061214        | Ji et al., 2021      | Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as add-on to metformin in patients with type 2 diabetes in SUSTAIN China: a 30-week, double-blind, phase 3a, randomized trial                                                                                | Study of patients with 1 to 2 OADs.<br><b>Details:</b> Participants with T2DM inadequately controlled on metformin were randomized to receive semaglutide 0.5 mg and sitagliptin placebo, semaglutide 1.0 mg and sitagliptin placebo, sitagliptin 100 mg and semaglutide placebo (0.5 mg), or sitagliptin 100 mg and semaglutide placebo (1.0 mg).                                                                                                                                          |

| Study ID                 | Clinical trial No. | Author, year                     | Title                                                                                                                                                                                                                                                     | Reason/detail for exclusion                                                                                                                                                       |
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| SUSTAIN FORTE            | NCT03989232        | Frías et al., 2021               | Efficacy and safety of once-weekly semaglutide 2.0 mg versus 1.0 mg in patients with type 2 diabetes (SUSTAIN FORTE): a double-blind, randomised, phase 3B trial                                                                                          | Study of patients with 1 to 2 OADs.<br><b>Details:</b> Participants on a stable dose of metformin with or without SU were randomly assigned to 2.0 mg or 1.0 QW s.c. semaglutide. |
| Abdul-Ghani et al., 2018 | NR                 | Abdul-Ghani et al., 2018         | Effect of combination therapy with liraglutide plus canagliflozin on HGP and HbA1c vs. each therapy alone in T2DM                                                                                                                                         | Study with unclear or mixed background therapy                                                                                                                                    |
| Ali et al., 2020         | NCT02324842        | Ali et al., 2020                 | Combination therapy with canagliflozin plus liraglutide exerts additive effect on weight loss, but not on HbA1c, in patients with type 2 diabetes                                                                                                         | Study with unclear or mixed background therapy                                                                                                                                    |
| Ando et al., 2021        | UMIN000019382      | Ando et al., 2021                | Simplification of complex insulin regimens using canagliflozin or liraglutide in patients with well-controlled type 2 diabetes: a 24-week randomized controlled trial                                                                                     | Study with unclear or mixed background therapy                                                                                                                                    |
| Arturi et al., 2017      | NR                 | Arturi et al., 2017              | Liraglutide improves cardiac function in patients with type 2 diabetes and chronic heart failure                                                                                                                                                          | Study with unclear or mixed background therapy                                                                                                                                    |
| AWARD-4                  | NCT01191268        | Lilly CSR<br>Blonde et al., 2015 | GBDD CSR<br>Once-weekly dulaglutide versus bedtime insulin glargine, both in combination with prandial insulin lispro, in patients with type 2 diabetes (AWARD-4): a randomised, open-label, phase 3, non-inferiority study                               | Study with unclear or mixed background therapy                                                                                                                                    |
| AWARD-8                  | NCT01769378        | Lilly CSR<br>Dungan et al., 2016 | GBDG CSR<br>A 24-week study to evaluate the efficacy and safety of once-weekly dulaglutide added on to glimepiride in type 2 diabetes (AWARD-8)                                                                                                           | Study with unclear or mixed background therapy                                                                                                                                    |
| Barnett et al., 2007     | NCT00099619        | Barnett et al., 2007             | Tolerability and efficacy of exenatide and titrated insulin glargine in adult patients with type 2 diabetes previously uncontrolled with metformin or a sulfonylurea: a multinational, randomized, open-label, two-period, crossover noninferiority trial | Study with unclear or mixed background therapy                                                                                                                                    |
| Bojer et al., 2021       | NCT02655770        | Bojer et al., 2021               | Metabolic improvement with short-term, glucagon-like peptide-1 receptor agonist treatment does not improve cardiac diastolic dysfunction in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial                           | Study with unclear or mixed background therapy                                                                                                                                    |
| Bouchi et al., 2017      | UMIN000015867      | Bouchi et al., 2017              | Reduction of visceral fat by liraglutide is associated with ameliorations of hepatic steatosis, albuminuria, and micro-inflammation in type 2 diabetic patients with insulin treatment: a randomized controlled trial                                     | Study with unclear or mixed background therapy                                                                                                                                    |
| Buse et al., 2004        | NR                 | Buse et al., 2004                | Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes                                                                                                                                  | Study with unclear or mixed background therapy                                                                                                                                    |
| Carlson et al., 2019     | NR                 | Carlson et al., 2019             | Evaluation of insulin glargine and exenatide alone and in combination: a randomized clinical trial with continuous glucose monitoring and ambulatory glucose profile analysis                                                                             | Study with unclear or mixed background therapy                                                                                                                                    |
| Davis et al., 2007       | NCT00099333        | Davis et al., 2007               | Exploring the substitution of exenatide for insulin in patients with type 2 diabetes treated with insulin in combination with oral antidiabetes agents                                                                                                    | Study with unclear or mixed background therapy                                                                                                                                    |
| Diamant et al., 2014(b)  | NCT00960661        | Diamant et al., 2014(b)          | Glucagon-like peptide 1 receptor agonist or bolus insulin with optimized basal insulin in type 2 diabetes                                                                                                                                                 | Study with unclear or mixed background therapy                                                                                                                                    |
| DUAL 1 Japan             | NCT02607306        | Kaku et al., 2019                | Superior efficacy with a fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with insulin degludec and liraglutide in insulin-naïve Japanese patients with type 2 diabetes in a phase 3, open-label, randomized trial         | Study with unclear or mixed background therapy                                                                                                                                    |
| DURATION NEO-1           | NCT01652716        | Wysham et al., 2018              | Efficacy and tolerability of the new autoinjected suspension of exenatide once weekly versus exenatide twice daily in patients with type 2 diabetes                                                                                                       | Study with unclear or mixed background therapy                                                                                                                                    |

| Study ID           | Clinical trial No.     | Author, year            | Title                                                                                                                                                                                                                                                                                                     | Reason/detail for exclusion                    |
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| DURATION-1         | NCT00308139            | Drucker et al., 2008    | Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study                                                                                                                                                                            | Study with unclear or mixed background therapy |
| DURATION-5         | NCT00877890            | Blevins et al., 2011    | DURATION-5: exenatide once weekly resulted in greater improvements in glycemic control compared with exenatide twice daily in patients with type 2 diabetes                                                                                                                                               | Study with unclear or mixed background therapy |
| ELEGANT            | NCT01392898            | de Wit et al., 2016     | Durable efficacy of liraglutide in patients with type 2 diabetes and pronounced insulin-associated weight gain: 52-week results from the Effect of Liraglutide on insulin-associated wEight GAIN in patients with Type 2 diabetes' (ELEGANT) randomized controlled trial                                  | Study with unclear or mixed background therapy |
| EXENDA             | EudraCT 2016-000574-38 | Harreiter et al., 2021  | Combined exenatide and dapagliflozin has no additive effects on reduction of hepatocellular lipids despite better glycaemic control in patients with type 2 diabetes mellitus treated with metformin: EXENDA, a 24-week, prospective, randomized, placebo-controlled pilot trial                          | Study with unclear or mixed background therapy |
| Frias et al., 2019 | NR                     | Frias et al., 2019      | Efficacy and safety of an expanded dulaglutide dose range: a phase 2, placebo-controlled trial in patients with type 2 diabetes using metformin                                                                                                                                                           | Study with unclear or mixed background therapy |
| Gao et al., 2009   | NCT00324363            | Gao et al., 2009        | Efficacy and safety of exenatide in patients of Asian descent with type 2 diabetes inadequately controlled with metformin or metformin and a sulphonylurea                                                                                                                                                | Study with unclear or mixed background therapy |
| Gao et al., 2020   | NCT02477969            | Gao et al., 2020        | Efficacy and safety of polyethylene glycol loxanatide as add-on to metformin in patients with type 2 diabetes: a multicentre, randomized, double-blind, placebo-controlled, phase 3b trial                                                                                                                | Study with unclear or mixed background therapy |
| GetGoal Duo-2      | NCT01768559            | Rosenstock et al., 2016 | Prandial options to advance basal insulin glargine therapy: testing lixisenatide plus basal insulin versus insulin glulisine either as basal-plus or basal-bolus in type 2 diabetes: the GetGoal Duo-2 trial                                                                                              | Study with unclear or mixed background therapy |
| GetGoal-O          | NCT01798706            | Meneilly et al., 2017   | Lixisenatide therapy in older patients with type 2 diabetes inadequately controlled on their current antidiabetic treatment: the GetGoal-O randomized trial                                                                                                                                               | Study with unclear or mixed background therapy |
| GRAVITAS           | ISRCTN13643081         | Miras et al., 2019      | Adjunctive liraglutide treatment in patients with persistent or recurrent type 2 diabetes after metabolic surgery (GRAVITAS): a randomised, double-blind, placebo-controlled trial                                                                                                                        | Study with unclear or mixed background therapy |
| HARMONY 6          | NCT00976391            | Rosenstock et al., 2014 | Advancing basal insulin replacement in type 2 diabetes inadequately controlled with insulin glargine plus oral agents: a comparison of adding albiglutide, a weekly GLP-1 receptor agonist, versus thrice-daily prandial insulin lispro                                                                   | Study with unclear or mixed background therapy |
|                    |                        | Leiter et al., 2017     | Once weekly glucagon-like peptide-1 receptor agonist albiglutide vs. prandial insulin added to basal insulin in patients with type 2 diabetes mellitus: results over 52 weeks                                                                                                                             |                                                |
| HARMONY 8          | NCT01098539            | Leiter et al., 2014     | Efficacy and safety of the once-weekly GLP-1 receptor agonist albiglutide versus sitagliptin in patients with type 2 diabetes and renal impairment: a randomized phase III study                                                                                                                          | Study with unclear or mixed background therapy |
| HARMONY 1          | NCT00849056            | Reusch et al., 2014     | Efficacy and safety of once-weekly glucagon-like peptide 1 receptor agonist albiglutide (HARMONY 1 trial): 52-week primary endpoint results from a randomized, double-blind, placebo-controlled trial in patients with type 2 diabetes mellitus not controlled on pioglitazone, with or without metformin | Study with unclear or mixed background therapy |
| HARMONY 2          | NCT00849017            | Nauck et al., 2016(a)   | Efficacy and safety of once-weekly GLP-1 receptor agonist albiglutide (HARMONY 2): 52 week primary endpoint results from a randomised, placebo-                                                                                                                                                           | Study with unclear or mixed background therapy |

| Study ID                | Clinical trial No. | Author, year            | Title                                                                                                                                                                                                                                                             | Reason/detail for exclusion                    |
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|                         |                    |                         | controlled trial in patients with type 2 diabetes mellitus inadequately controlled with diet and exercise                                                                                                                                                         |                                                |
| HARMONY 3               | NCT00838903        | Ahrén et al., 2014      | HARMONY 3: 104-week randomized, double-blind, placebo- and active-controlled trial assessing the efficacy and safety of albiglutide compared with placebo, sitagliptin, and glimepiride in patients with type 2 diabetes taking metformin                         | Study with unclear or mixed background therapy |
| HARMONY 4               | NCT00838916        | Weissman et al., 2014   | HARMONY 4: randomised clinical trial comparing once-weekly albiglutide and insulin glargine in patients with type 2 diabetes inadequately controlled with metformin with or without sulfonylurea                                                                  | Study with unclear or mixed background therapy |
| HARMONY 5               | NCT00839527        | Home et al., 2015       | Efficacy and tolerability of albiglutide versus placebo or pioglitazone over 1 year in people with type 2 diabetes currently taking metformin and glimepiride: HARMONY 5                                                                                          | Study with unclear or mixed background therapy |
| Hygum et al., 2020      | NCT02473809        | Hygum et al., 2020      | Bone resorption is unchanged by liraglutide in type 2 diabetes patients: a randomised controlled trial                                                                                                                                                            | Study with unclear or mixed background therapy |
| Ikonomidis et al., 2020 | NCT03878706        | Ikonomidis et al., 2020 | Effects of glucagon-like peptide-1 receptor agonists, sodium-glucose cotransporter-2 inhibitors, and their combination on endothelial glycocalyx, arterial function, and myocardial work index in patients with type 2 diabetes mellitus after 12-month treatment | Study with unclear or mixed background therapy |
| Ishii et al., 2019      | NCT02750410        | Ishii et al., 2020      | Once-weekly dulaglutide with insulin therapy for type 2 diabetes: efficacy and safety results from a phase 4, randomized, placebo-controlled study                                                                                                                | Study with unclear or mixed background therapy |
| Jaiswal et al., 2015    | NCT00855439        | Jaiswal et al., 2015    | Effects of exenatide on measures of diabetic neuropathy in subjects with type 2 diabetes: results from an 18-month proof-of-concept open-label randomized study                                                                                                   | Study with unclear or mixed background therapy |
| JDDM 33                 | UMIN000004970      | Yokoyama et al., 2014   | Liraglutide versus sitagliptin in a 24-week, multicenter, open-label, randomized, parallel-group study in Japanese type 2 diabetes mellitus patients responding inadequately to a sulfonylurea and/or one or two other oral antidiabetic drugs (JDDM 33)          | Study with unclear or mixed background therapy |
| Joubert et al., 2021    | NCT01140893        | Joubert et al., 2021    | Efficacy and safety of exenatide as add-on therapy for patients with type 2 diabetes with an intensive insulin regimen: a randomized double-blind trial                                                                                                           | Study with unclear or mixed background therapy |
| Kaku et al., 2010       | NCT00395746        | Kaku et al., 2010       | Improved glycaemic control with minimal hypoglycaemia and no weight change with the once-daily human glucagon-like peptide-1 analogue liraglutide as add-on to sulphonylurea in Japanese patients with type 2 diabetes                                            | Study with unclear or mixed background therapy |
|                         |                    | Seino et al., 2011      | Glucagon-like peptide-1 analog liraglutide in combination with sulfonylurea safely improves blood glucose measures vs sulfonylurea monotherapy in Japanese patients with type 2 diabetes: results of a 52-week, randomized, multicenter trial                     |                                                |
| KIND-LM                 | UMIN000004243      | Tanaka et al., 2015     | Effects of liraglutide monotherapy on beta cell function and pancreatic enzymes compared with metformin in Japanese overweight/obese patients with type 2 diabetes mellitus: a subpopulation analysis of the KIND-LM randomized trial                             | Study with unclear or mixed background therapy |
| Koska et al., 2021      | NCT02162550        | Koska et al., 2021      | The effect of exenatide once weekly on carotid atherosclerosis in individuals with type 2 diabetes: an 18-month randomized placebo-controlled study                                                                                                               | Study with unclear or mixed background therapy |
| LEAD-1                  | NR                 | Marre et al., 2009      | Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with type 2 diabetes (LEAD-1 SU)                   | Study with unclear or mixed background therapy |

| Study ID                 | Clinical trial No.     | Author, year            | Title                                                                                                                                                                                                                         | Reason/detail for exclusion                    |
|--------------------------|------------------------|-------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|
| LIBRA                    | NCT01270789            | Retnakaran et al., 2014 | Liraglutide and the preservation of pancreatic $\beta$ -cell function in early type 2 diabetes: the LIBRA trial                                                                                                               | Study with unclear or mixed background therapy |
| LIPER2                   | EudraCT 2012-005197-63 | Wagner et al., 2019     | Effect of liraglutide on physical performance in type 2 diabetes: results of a randomized, double-blind, controlled trial (LIPER2)                                                                                            | Study with unclear or mixed background therapy |
| LIRAFLAME                | NCT03449654            | Rasmussen et al., 2021  | Liraglutide reduces cardiac adipose tissue in type 2 diabetes: a secondary analysis of the LIRAFLAME randomized placebo-controlled trial                                                                                      | Study with unclear or mixed background therapy |
| Lou et al., 2020         | NR                     | Lou et al., 2020        | Liraglutide improves postprandial blood glucose, blood glucose levels, insulin resistance and physical distribution of T2DM patients with MS                                                                                  | Study with unclear or mixed background therapy |
| MAGNA VICTORIA           | NCT01761318            | Bizino et al., 2019     | Effect of liraglutide on cardiac function in patients with type 2 diabetes mellitus: randomized placebo-controlled trial                                                                                                      | Study with unclear or mixed background therapy |
| Martinez et al., 2017    | NR                     | Martinez et al., 2017   | Glycaemic control and beta cell function in type 2 diabetes on SGLT2i and GLP-1RA combination therapy                                                                                                                         | Study with unclear or mixed background therapy |
| Matikainen et al., 2018  | NCT02765399            | Matikainen et al., 2019 | Liraglutide treatment improves postprandial lipid metabolism and cardiometabolic risk factors in humans with adequately controlled type 2 diabetes: a single-centre randomized controlled study                               | Study with unclear or mixed background therapy |
| MDI Liraglutide          | EudraCT 2012-001941-42 | Lind et al., 2015       | Liraglutide in people treated for type 2 diabetes with multiple daily insulin injections: randomised clinical trial (MDI Liraglutide trial)                                                                                   | Study with unclear or mixed background therapy |
| Mensberg et al., 2017    | NCT01455441            | Mensberg et al., 2017   | Near-normalization of glycaemic control with glucagon-like peptide-1 receptor agonist treatment combined with exercise in patients with type 2 diabetes                                                                       | Study with unclear or mixed background therapy |
| Nagaike et al., 2019     | UMIN000034353          | Nagaike et al., 2019    | Effect of dulaglutide versus liraglutide on glucose variability, oxidative stress, and endothelial function in type 2 diabetes: a prospective study                                                                           | Study with unclear or mixed background therapy |
| Nakaguchi et al., 2020   | UMIN000027614          | Nakaguchi et al., 2020  | Effects of liraglutide and empagliflozin added to insulin therapy in patients with type 2 diabetes: a randomized controlled study                                                                                             | Study with unclear or mixed background therapy |
| Nino et al., 2017        | NCT01733758            | Nino et al., 2017       | Weekly glucagon-like peptide-1 receptor agonist albiglutide as monotherapy improves glycemic parameters in Japanese patients with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled study              | Study with unclear or mixed background therapy |
| Nyström et al., 2017     | NCT01425580            | Nyström et al., 2017    | Effects on subclinical heart failure in type 2 diabetic subjects on liraglutide treatment vs. glimepiride both in combination with metformin: a randomized open parallel-group study                                          | Study with unclear or mixed background therapy |
| Pasquel et al., 2021     | NCT01919489            | Pasquel et al., 2021    | Liraglutide hospital discharge trial: a randomized controlled trial comparing the safety and efficacy of liraglutide versus insulin glargine for the management of patients with type 2 diabetes after hospital discharge     | Study with unclear or mixed background therapy |
| Ripa et al., EASD 2020   | NCT03449654            | Ripa et al., 2020       | Liraglutide and vascular inflammation in type 2 diabetes as assessed by FDG-PET/CT: the LiraFlame study                                                                                                                       | Study with unclear or mixed background therapy |
| Rosenstock et al., 2009( | NCT00518115            | Rosenstock et al., 2009 | Potential of albiglutide, a long-acting GLP-1 receptor agonist, in type 2 diabetes: a randomized controlled trial exploring weekly, biweekly, and monthly dosing                                                              | Study with unclear or mixed background therapy |
| Rosenstock et al., 2020  | NCT02229227            | Rosenstock et al., 2020 | Impact of a weekly glucagon-like peptide 1 receptor agonist, albiglutide, on glycemic control and on reducing prandial insulin use in type 2 diabetes inadequately controlled on multiple insulin therapy: a randomized trial | Study with unclear or mixed background therapy |
|                          |                        | Rosenstock et al., 2018 | Near-normoglycemia, with meaningful discontinuations of prandial insulin, by adding weekly albiglutide (Albi) to uncontrolled basal/bolus insulin-treated type 2 diabetes (T2DM)                                              |                                                |

| Study ID                  | Clinical trial No. | Author, year              | Title                                                                                                                                                                                                                                                                                        | Reason/detail for exclusion                                                                                                                                                                                                                                                                                                                                                    |
|---------------------------|--------------------|---------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Savvidou et al., 2016     | NR                 | Savvidou et al., 2016     | Circulating adiponectin levels in type 2 diabetes mellitus patients with or without non-alcoholic fatty liver disease: results of a small, open-label, randomized controlled intervention trial in a subgroup receiving short-term exenatide                                                 | Study with unclear or mixed background therapy                                                                                                                                                                                                                                                                                                                                 |
| SCALE                     | NCT01272232        | Davies et al., 2015       | Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE diabetes randomized clinical trial                                                                                                                                                                    | Study with unclear or mixed background therapy                                                                                                                                                                                                                                                                                                                                 |
| Seino et al., 2014        | NCT01098461        | Seino et al., 2014        | A randomized dose-finding study demonstrating the efficacy and tolerability of albiglutide in Japanese patients with type 2 diabetes mellitus                                                                                                                                                | Study with unclear or mixed background therapy                                                                                                                                                                                                                                                                                                                                 |
| Seino et al., 2010        | NCT00393718        | Seino et al., 2010        | Efficacy and safety of the once-daily human GLP-1 analogue, liraglutide, vs glibenclamide monotherapy in Japanese patients with type 2 diabetes                                                                                                                                              | Study with unclear or mixed background therapy                                                                                                                                                                                                                                                                                                                                 |
|                           |                    | Kaku et al., 2011         | Fifty-two-week, randomized, multicenter trial to compare the safety and efficacy of the novel glucagon-like peptide-1 analog liraglutide vs glibenclamide in patients with type 2 diabetes                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                |
| Seino et al., 2016        | NCT01572740        | Seino et al., 2016        | Combination therapy with liraglutide and insulin in Japanese patients with type 2 diabetes: a 36-week, randomized, double-blind, parallel-group trial                                                                                                                                        | Study with unclear or mixed background therapy                                                                                                                                                                                                                                                                                                                                 |
| Shuai et al., 2021        | NCT02477865        | Shuai et al., 2021        | Efficacy and safety of polyethylene glycol lixenatide monotherapy in type 2 diabetes patients: a multicentre, randomized, double-blind, placebo-controlled phase 3a clinical trial                                                                                                           | Study with unclear or mixed background therapy                                                                                                                                                                                                                                                                                                                                 |
| SURPASS J-combo           | NCT03861039        | Lilly CSR 2021            | GPGP CSR                                                                                                                                                                                                                                                                                     | Study with unclear or mixed background therapy; Kadowaki T, Chin R, Ozeki A, Imaoka T, Ogawa Y. Safety and efficacy of tirzepatide as an add-on to single oral antihyperglycaemic medication in patients with type 2 diabetes in Japan (SURPASS J-combo): a multicentre, randomised, open-label, parallel-group, phase 3 trial. Lancet Diabetes Endocrinol. 2022;10(9):634–44. |
| Suzuki et al., 2014       | NR                 | Suzuki et al., 2014       | Greater efficacy and improved endothelial dysfunction in untreated type 2 diabetes with liraglutide versus sitagliptin                                                                                                                                                                       | Study with unclear or mixed background therapy                                                                                                                                                                                                                                                                                                                                 |
| van Eyk et al., 2019      | NCT02660047        | van Eyk et al., 2019      | A double-blind, placebo-controlled, randomised trial to assess the effect of liraglutide on ectopic fat accumulation in South Asian type 2 diabetes patients                                                                                                                                 | Study with unclear or mixed background therapy                                                                                                                                                                                                                                                                                                                                 |
| Vanderheiden et al., 2016 | NCT01505673        | Vanderheiden et al., 2016 | Effect of adding liraglutide vs placebo to a high-dose insulin regimen in patients with type 2 diabetes a randomized clinical trial                                                                                                                                                          | Study with unclear or mixed background therapy                                                                                                                                                                                                                                                                                                                                 |
| Wang et al., 2020(b)      | NCT02449603        | Wang et al., 2020(b)      | Comparison of blood glucose variability between exenatide and biphasic insulin aspart 30 in Chinese participants with type 2 diabetes inadequately controlled with metformin monotherapy: a multicenter, open-label, randomized trial                                                        | Study with unclear or mixed background therapy                                                                                                                                                                                                                                                                                                                                 |
| Wang et al., 2020(c)      | NR                 | Wang et al., 2020 (c)     | Comparison between the effects of sitagliptin and liraglutide on blood glucose and cognitive function of patients with both type 2 diabetes mellitus and post-stroke mild cognitive impairment                                                                                               | Study with unclear or mixed background therapy                                                                                                                                                                                                                                                                                                                                 |
| Wu et al., 2011           | NR                 | Wu et al., 2011           | Effect of exenatide on inflammatory and oxidative stress markers in patients with type 2 diabetes mellitus                                                                                                                                                                                   | Study with unclear or mixed background therapy                                                                                                                                                                                                                                                                                                                                 |
| Yang et al., 2011         | NR                 | Yang et al., 2011         | Liraglutide provides similar glycaemic control as glimepiride (both in combination with metformin) and reduces body weight and systolic blood pressure in Asian population with type 2 diabetes from China, South Korea and India: a 16-week, randomized, double-blind, active control trial | Study with unclear or mixed background therapy                                                                                                                                                                                                                                                                                                                                 |

| Study ID                                                                            | Clinical trial No. | Author, year         | Title                                                                                                                                                                                                  | Reason/detail for exclusion                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|-------------------------------------------------------------------------------------|--------------------|----------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Yin et al., 2018                                                                    | NCT02325960        | Yin et al., 2018     | Comparison of glycemic variability in Chinese T2DM patients treated with exenatide or insulin glargine: a randomized controlled trial                                                                  | Study with unclear or mixed background therapy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Zhang et al., 2012                                                                  | NR                 | Zhang et al., 2012   | Exenatide reduces urinary transforming growth factor-β1 and type IV collagen excretion in patients with type 2 diabetes and microalbuminuria                                                           | Study with unclear or mixed background therapy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Zhang et al., 2020                                                                  | ChiCTR-1800015658  | Zhang et al., 2020   | Comparison of the effects of twice-daily exenatide and insulin on carotid intima-media thickness in type 2 diabetes mellitus patients: a 52-week randomized, open-label, controlled trial              | Study with unclear or mixed background therapy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Zinman et al., 2007                                                                 | NCT00099320        | Zinman et al., 2007  | The effect of adding exenatide to a thiazolidinedione in suboptimally controlled type 2 diabetes: a randomized trial                                                                                   | Study with unclear or mixed background therapy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Davies et al., 2017                                                                 | NCT01923181        | Davies et al., 2017  | Effect of oral semaglutide compared with placebo and subcutaneous semaglutide on glycemic control in patients with type 2 diabetes: a randomized clinical trial                                        | Study with unclear or mixed background therapy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Kaku et al., 2018                                                                   | NCT02207374        | Kaku et al., 2018    | Safety and efficacy of once-weekly semaglutide vs additional oral antidiabetic drugs in Japanese people with inadequately controlled type 2 diabetes: a randomized trial                               | Study with unclear or mixed background therapy.<br><b>Details:</b> Randomized to receive semaglutide 0.5 mg or 1.0 mg QW or 1 additional OAD (DPP-4 inhibitor, biguanide, SU, glinide, α-glucosidase inhibitor, or thiazolidinedione) with a different mode of action from that of background therapy.                                                                                                                                                                                                                                                                                                                                                                   |
| Lingvay et al., 2018                                                                | NCT02461589        | Lingvay et al., 2018 | A 26-week randomized controlled trial of semaglutide once daily versus liraglutide and placebo in patients with type 2 diabetes suboptimally controlled on diet and exercise with or without metformin | Study with unclear or mixed background therapy.<br><b>Details:</b> Patients were randomized to semaglutide:liraglutide:placebo in 1 of 4 volume-matched doses and randomly assigned into 1 of 12 treatment arms in a 2:2:1 ratio (semaglutide: liraglutide:placebo) within each of the 4 dosing levels (50, 100, 200, and 300 µL) or to an additional 13th semaglutide treatment arm with the same number of patients as the active treatment arms. Semaglutide, liraglutide, and placebo were visually identical to fulfil the requirements for double-blind procedures, and equal volumes of semaglutide, liraglutide, and placebo were administered during treatment. |
| PIONEER 10                                                                          | NCT03015220        | Yabe et al., 2020    | Safety and efficacy of oral semaglutide versus dulaglutide in Japanese patients with type 2 diabetes (PIONEER 10): an open-label, randomized, active-controlled, phase 3a trial                        | Study with unclear or mixed background therapy.<br><b>Details:</b> Randomly assigned to receive QD oral semaglutide 3, 7, or 14 mg or QW s.c. dulaglutide 0.75 mg for 52 wk, as an add-on to their background medication.                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| STEP 2                                                                              | NCT03552757        | Davies et al., 2021  | Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial                         | Study with unclear or mixed background therapy.<br><b>Details:</b> Randomly allocated, stratified by background glucose-lowering medication and HbA1c, to s.c. injection of semaglutide 2.4 mg, semaglutide 1.0 mg, or visually matched placebo QW for 68 wk, plus a lifestyle intervention.                                                                                                                                                                                                                                                                                                                                                                             |
| <b>Study design or insulin titration scheme not comparable to SURPASS-5 (n = 2)</b> |                    |                      |                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| SUSTAIN 5                                                                           | NCT02305381        | Rodbard et al., 2018 | Semaglutide added to basal insulin in type 2 diabetes (SUSTAIN 5): a randomized, controlled trial                                                                                                      | Insulin titration not comparable to SURPASS-5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| Study ID                                      | Clinical trial No. | Author, year           | Title                                                                                                                                                                                                                                       | Reason/detail for exclusion                                                                                                                |
|-----------------------------------------------|--------------------|------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| PIONEER 8                                     | NCT03021187        | Zinman et al., 2019(a) | Efficacy, safety, and tolerability of oral semaglutide versus placebo added to insulin with or without metformin in patients with type 2 diabetes: the PIONEER 8 trial                                                                      | Study design not comparable with SURPASS-5                                                                                                 |
| <b>Study not meeting NMA criteria (n = 1)</b> |                    |                        |                                                                                                                                                                                                                                             |                                                                                                                                            |
| SIMPLE                                        | NCT01966978        | Abreu et al., 2019     | A randomized trial comparing the efficacy and safety of treating patients with type 2 diabetes and highly elevated HbA1c levels with basal-bolus insulin or a glucagon-like peptide-1 receptor agonist plus basal insulin: the SIMPLE study | Not meeting NMA criteria<br><b>Details:</b> Liraglutide 1.8 mg was compared with insulin aspart and did not connect with other treatments. |

The publication listed first for each study is the primary publication. One study has been referenced for each trial.

CSR Clinical study report, CVOT Cardiovascular outcomes trial, d Day(s), DPP-4 Dipeptidyl peptidase-4, FDG-PET/CT Fludeoxyglucose positron emission tomography/computed tomography, GLP-1 Glucagon-like peptide-1, HbA1c Glycated haemoglobin, HGP Hepatic glucose production, MS Multiple sclerosis, NR Not reported, OAD Oral antidiabetes drug, QD Once daily, QW Once weekly, s.c. Subcutaneous(ly), SGLT2 Sodium-glucose cotransporter-2, SU Sulphonylurea, T2DM Type 2 diabetes mellitus, wk Week(s).

### 3. Risk of Bias

**Table S3.1** Risk of bias assessment for studies included in the network meta-analysis

| Study             | Randomization | Allocation concealment | Blinding | Withdrawals | Outcome selection and reporting | Statistical methods <sup>a</sup> |
|-------------------|---------------|------------------------|----------|-------------|---------------------------------|----------------------------------|
| AWARD-9           | LR            | LR                     | LR       | LR          | LR                              |                                  |
| Buse et al., 2011 | LR            | LR                     | LR       | LR          | LR                              |                                  |
| DURATION-7        | LR            | LR                     | LR       | LR          | LR                              |                                  |
| GetGoal-Duo 1     | LR            | LR                     | LR       | LR          | LR                              |                                  |
| GetGoal-L         | LR            | LR                     | LR       | LR          | LR                              |                                  |
| SURPASS-5         | LR            | LR                     | LR       | LR          | LR                              | LR                               |

CRD Centre for Reviews and Dissemination, *LR* Low risk.

<sup>a</sup>The studies included in the systematic literature review were assessed using the Cochrane risk of bias tool and the CRD tool, and responses were consolidated as presented above. Responses relating to statistical methodology are only available for studies that were assessed using the CRD risk of bias tool. As such, responses for statistical methodology are not presented for studies that were assessed using the Cochrane risk of bias tool.

#### 4. Efficacy Matrix Tables

**Table S4.1** Change from baseline in HbA1c (%) at Week 40 (tirzepatide) versus Week 26 ( $\pm$  4 weeks) (comparators)

| Comparator           | Tirzepatide 5 mg     | Tirzepatide 10 mg    | Tirzepatide 15 mg    |
|----------------------|----------------------|----------------------|----------------------|
| Placebo              | -1.30 (-1.52, -1.08) | -1.66 (-1.88, -1.44) | -1.66 (-1.89, -1.44) |
| Tirzepatide 5 mg QW  | —                    | -0.36 (-0.58, -0.13) | -0.36 (-0.59, -0.13) |
| Tirzepatide 10 mg QW | 0.36 (0.13, 0.58)    | —                    | 0.00 (-0.23, 0.23)   |
| Tirzepatide 15 mg QW | 0.36 (0.13, 0.59)    | 0.00 (-0.23, 0.23)   | —                    |
| Dulaglutide 1.50 mg  | -0.53 (-0.87, -0.20) | -0.89 (-1.22, -0.56) | -0.89 (-1.23, -0.55) |
| Exenatide 2 mg QW    | -0.57 (-0.88, -0.25) | -0.93 (-1.24, -0.62) | -0.93 (-1.25, -0.61) |
| Exenatide 10 mcg BID | -0.60 (-0.93, -0.27) | -0.96 (-1.29, -0.62) | -0.96 (-1.3, -0.62)  |
| Lixisenatide 20 mcg  | -1.00 (-1.3, -0.71)  | -1.36 (-1.66, -1.07) | -1.36 (-1.66, -1.07) |

Data are shown as median difference (95% credible interval). Cells highlighted in green show comparisons that significantly favour tirzepatide (dose according to column header). Cells highlighted in red show comparisons that favour other tirzepatide doses or active treatments.

*BID* Twice daily, *HbA1c* Glycated haemoglobin, *QW* Once weekly.

**Table S4.2** Likelihood of patients reaching target HbA1c <7.0% at Week 40 (tirzepatide) versus Week 26 ( $\pm$  4 weeks) (comparators)

| Comparator           | Tirzepatide 5 mg     | Tirzepatide 10 mg     | Tirzepatide 15 mg    |
|----------------------|----------------------|-----------------------|----------------------|
| Placebo              | 27.33 (12.79, 66.10) | 80.44 (27.34, 362.45) | 32.36 (14.43, 84.43) |
| Tirzepatide 5 mg QW  | —                    | 2.93 (0.80, 14.45)    | 1.18 (0.41, 3.58)    |
| Tirzepatide 10 mg QW | 0.34 (0.07, 1.26)    | —                     | 0.40 (0.08, 1.55)    |
| Tirzepatide 15 mg QW | 0.85 (0.28, 2.46)    | 2.49 (0.65, 12.33)    | —                    |
| Dulaglutide 1.50 mg  | 6.79 (2.73, 18.38)   | 20.08 (5.97, 96.72)   | 8.02 (3.14, 23.33)   |
| Exenatide 2 mg QW    | 4.47 (1.69, 12.69)   | 13.18 (3.81, 64.65)   | 5.29 (1.93, 15.99)   |
| Exenatide 10 mcg BID | 9.96 (3.95, 27.42)   | 29.41 (8.75, 142.21)  | 11.64 (4.53, 34.69)  |
| Lixisenatide 20 mcg  | 12.50 (5.48, 31.92)  | 36.78 (11.91, 171.25) | 14.80 (6.21, 40.41)  |

Data are shown as odds ratio (95% credible interval). Cells highlighted in green show comparisons that significantly favour tirzepatide (dose according to column header).

*BID* Twice daily, *HbA1c* Glycated haemoglobin, *QW* Once weekly.

**Table S4.3** Likelihood of patients reaching target HbA1c  $\leq 6.5\%$  at Week 40 (tirzepatide) versus Week 26 ( $\pm 4$  weeks) (comparators)

| Comparator           | Tirzepatide 5 mg     | Tirzepatide 10 mg     | Tirzepatide 15 mg   |
|----------------------|----------------------|-----------------------|---------------------|
| Placebo              | 20.22 (10.65, 40.53) | 94.54 (38.34, 275.84) | 62.3 (27.9, 154.93) |
| Tirzepatide 5 mg QW  | —                    | 4.66 (1.91, 13.28)    | 3.07 (1.38, 7.36)   |
| Tirzepatide 10 mg QW | 0.21 (0.08, 0.52)    | —                     | 0.66 (0.21, 1.93)   |
| Tirzepatide 15 mg QW | 0.33 (0.14, 0.73)    | 1.52 (0.52, 4.77)     | —                   |
| Dulaglutide 1.50 mg  | 3.99 (1.72, 9.58)    | 18.7 (6.48, 61.06)    | 12.29 (4.61, 35.01) |
| Exenatide 10 mcg BID | 4.14 (1.64, 10.57)   | 19.42 (6.28, 66.52)   | 12.8 (4.46, 37.98)  |
| Lixisenatide 20 mcg  | 7.5 (3.52, 16.68)    | 35.07 (13.01, 110.29) | 23.08 (9.47, 62.69) |

Data are shown as odds ratio (95% credible interval). Cells highlighted in green show comparisons that significantly favour tirzepatide (dose according to column header). Cells highlighted in red show comparisons that favour other tirzepatide doses or active treatments.

*BID* Twice daily, *HbA1c* Glycated haemoglobin, *QW* Once weekly.

**Table S4.4** Change from baseline in weight (kg) at Week 40 (tirzepatide) versus Week 26 ( $\pm 4$  weeks) (comparators) in the main analysis and sensitivity analysis

| Comparator           | Tirzepatide 5 mg        |                         | Tirzepatide 10 mg        |                         | Tirzepatide 15 mg          |                           |
|----------------------|-------------------------|-------------------------|--------------------------|-------------------------|----------------------------|---------------------------|
|                      | Main                    | Sensitivity             | Main                     | Sensitivity             | Main                       | Sensitivity               |
| Placebo              | -7.90<br>(-9.50, -6.31) | -6.79<br>(-7.52, -6.07) | -9.90<br>(-11.48, -8.30) | -8.39<br>(-9.12, -7.67) | -12.60<br>(-14.23, -11.00) | -10.09<br>(-10.82, -9.36) |
| Tirzepatide 5 mg QW  | —                       | —                       | -2.00<br>(-3.59, -0.37)  | -1.59<br>(-2.32, -0.87) | -4.70<br>(-6.33, -3.09)    | -3.3<br>(-4.04, -2.55)    |
| Tirzepatide 10 mg QW | 2.00<br>(0.37, 3.59)    | 1.59<br>(0.87, 2.32)    | —                        | —                       | -2.7<br>(-4.34, -1.08)     | -1.71<br>(-2.44, -0.96)   |
| Tirzepatide 15 mg QW | 4.70<br>(3.09, 6.33)    | 3.3<br>(2.55, 4.04)     | 2.70<br>(1.08, 4.34)     | 1.71<br>(0.96, 2.44)    | —                          | —                         |
| Dulaglutide 1.50 mg  | -5.50<br>(-7.29, -3.70) | -4.42<br>(-5.52, -3.32) | -7.49<br>(-9.29, -5.70)  | -6.02<br>(-7.11, -4.93) | -10.20<br>(-12.02, -8.38)  | -7.73<br>(-8.83, -6.62)   |
| Exenatide 2 mg QW    | -6.40<br>(-8.14, -4.66) | -5.21<br>(-6.22, -4.2)  | -8.40<br>(-10.14, -6.64) | -6.81<br>(-7.82, -5.8)  | -11.10<br>(-12.87, -9.35)  | -8.52<br>(-9.53, -7.49)   |
| Exenatide 10 mcg BID | -5.16<br>(-7.05, -3.28) | -4.11<br>(-5.17, -3.04) | -7.17<br>(-9.04, -5.26)  | -5.7<br>(-6.77, -4.63)  | -9.87<br>(-11.78, -7.96)   | -7.41<br>(-8.47, -6.33)   |
| Lixisenatide 20 mcg  | -6.77<br>(-8.46, -5.10) | -5.25<br>(-6.55, -3.96) | -8.77<br>(-10.44, -7.09) | -6.85<br>(-8.15, -5.55) | -11.47<br>(-13.18, -9.78)  | -8.55<br>(-9.86, -7.25)   |

Data are shown as median difference (95% credible interval). Cells highlighted in green show comparisons that significantly favour tirzepatide (dose according to column header). Cells highlighted in red show comparisons that favour other tirzepatide doses or active treatments.

*BID* Twice daily, *HbA1c* Glycated haemoglobin, *QW* Once weekly.

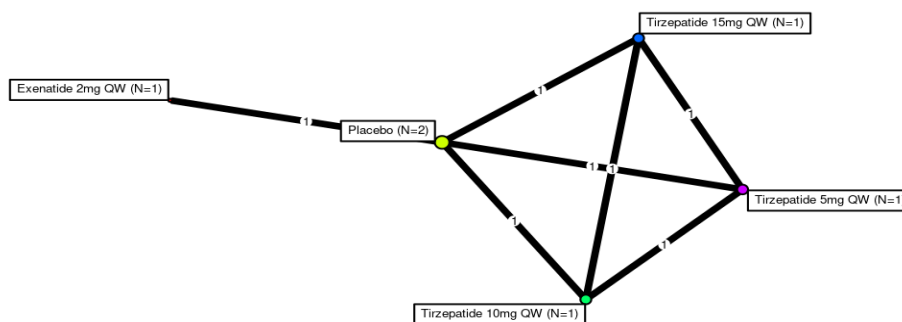
## 5. Other Efficacy Outcomes

### 5.1 Weight Loss

#### *Likelihood of Patients Reaching Weight Loss of $\geq 5\%$*

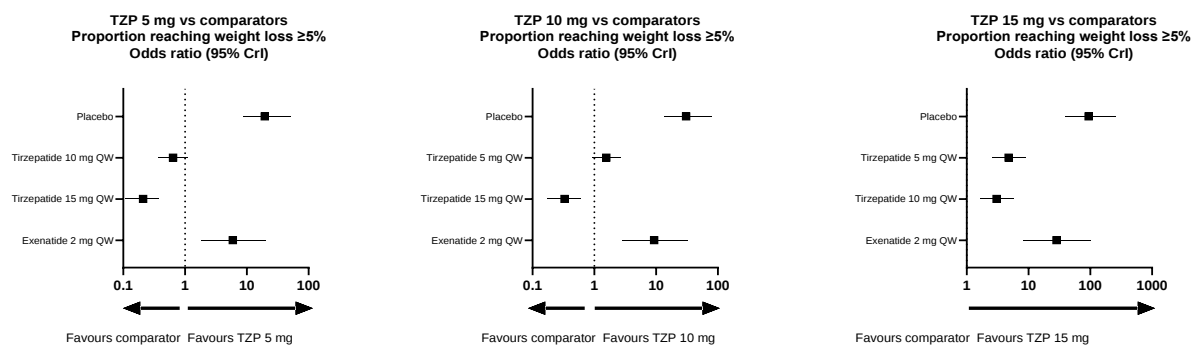
Two trials reported on the likelihood of patients reaching weight loss of  $\geq 5\%$  to Week 40 (tirzepatide) and Week 26 ( $\pm 4$  weeks) (comparators) (**Figures S5.1.1 and S5.1.2; Table S5.1.1**). Patients who received tirzepatide 5, 10, and 15 mg had a significantly greater likelihood of reaching weight loss of  $\geq 5\%$  compared with patients who received placebo or exenatide 2 mg.

**Figure S5.1.1** Main analysis network for likelihood of patients reaching weight loss of  $\geq 5\%$



QW Once weekly.

**Figure S5.1.2** Forest plots of change in body weight and likelihood of patients reaching weight loss of  $\geq 5\%$  from baseline to Week 40 (TZP) and Week 26 ( $\pm 4$  weeks) (comparators)



CrI Credible interval, QW Once weekly, TZP Tirzepatide.

**Table S5.1.1** Likelihood of patients reaching weight loss of  $\geq 5\%$  at Week 40 (tirzepatide) versus Week 26 ( $\pm 4$  weeks) (comparators)

| Comparator           | Tirzepatide 5 mg    | Tirzepatide 10 mg    | Tirzepatide 15 mg     |
|----------------------|---------------------|----------------------|-----------------------|
| Placebo              | 19.56 (8.78, 50.79) | 30.69 (13.69, 79.64) | 93.93 (39.57, 258.52) |
| Tirzepatide 5 mg QW  | —                   | 1.56 (0.92, 2.68)    | 4.78 (2.61, 9.11)     |
| Tirzepatide 10 mg QW | 0.64 (0.37, 1.09)   | —                    | 3.05 (1.65, 5.89)     |
| Tirzepatide 15 mg QW | 0.21 (0.11, 0.38)   | 0.33 (0.17, 0.61)    | —                     |
| Exenatide 2 mg QW    | 5.93 (1.8, 20.46)   | 9.28 (2.81, 32.16)   | 28.39 (8.25, 102.86)  |

Data are shown as odds ratio (95% credible interval). Cells highlighted in green show comparisons that significantly favour tirzepatide (dose according to column header). Cells highlighted in red show comparisons that favour other tirzepatide doses or active treatments.

QW Once weekly.

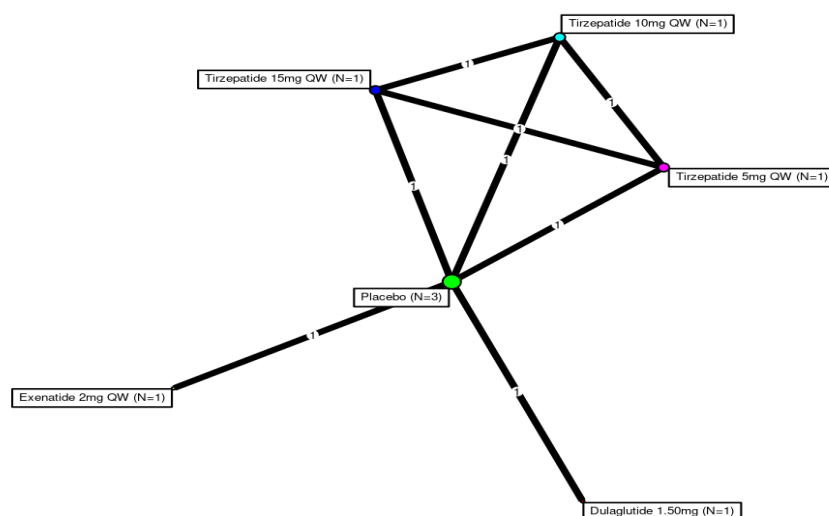
## 5.2 Lipoprotein

### *Change from Baseline in Low-Density Lipoprotein Cholesterol*

Three trials reported change from baseline in low-density lipoprotein (LDL) cholesterol to Week 40 (tirzepatide) and Week 26 ( $\pm 4$  weeks) (comparators) (**Figures S5.2.1 and S5.2.2; Table S5.2.1**).

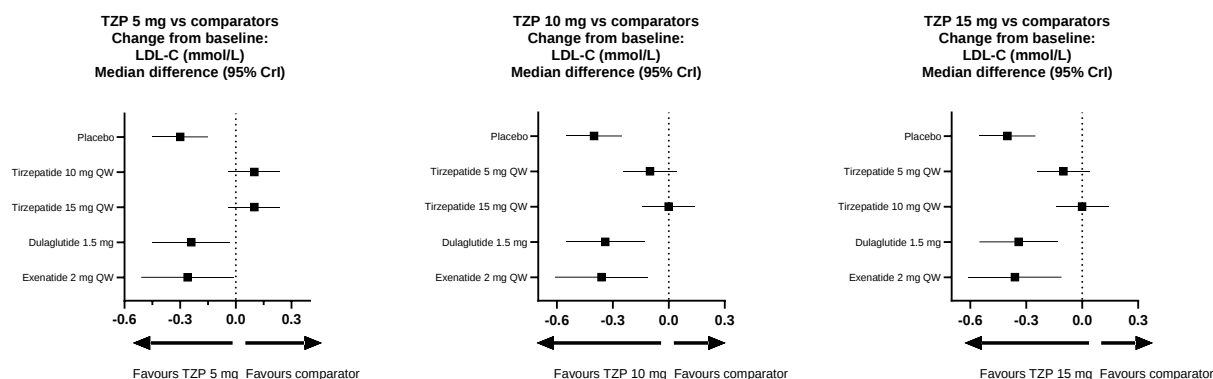
Tirzepatide 5, 10, and 15 mg showed significantly greater reductions in LDL cholesterol from baseline compared with placebo, dulaglutide 1.50 mg, and exenatide 2 mg.

**Figure S5.2.1** Main analysis network for change from baseline in low-density lipoprotein cholesterol



QW Once weekly.

**Figure S5.2.2** Forest plots of change from baseline in low-density lipoprotein cholesterol (mmol/L) to Week 40 (TZP) and Week 26 ( $\pm$  4 weeks) (comparators)



CrI Credible interval, LDL-C Low-density lipoprotein cholesterol, QW Once weekly, TZP Tirzepatide.

**Table S5.2.1** Change from baseline in low-density lipoprotein cholesterol (mmol/L) to Week 40 (tirzepatide) versus Week 26 ( $\pm$  4 weeks) (comparators)

| Comparator           | Tirzepatide 5 mg     | Tirzepatide 10 mg    | Tirzepatide 15 mg    |
|----------------------|----------------------|----------------------|----------------------|
| Placebo              | -0.30 (-0.45, -0.15) | -0.40 (-0.55, -0.25) | -0.40 (-0.55, -0.25) |
| Tirzepatide 5 mg QW  | —                    | -0.10 (-0.24, 0.04)  | -0.10 (-0.24, 0.04)  |
| Tirzepatide 10 mg QW | 0.10 (-0.04, 0.24)   | —                    | 0.00 (-0.14, 0.14)   |
| Tirzepatide 15 mg QW | 0.10 (-0.04, 0.24)   | 0.00 (-0.14, 0.14)   | —                    |
| Dulaglutide 1.50 mg  | -0.24 (-0.45, -0.03) | -0.34 (-0.55, -0.13) | -0.34 (-0.55, -0.13) |
| Exenatide 2 mg QW    | -0.26 (-0.51, -0.01) | -0.36 (-0.61, -0.11) | -0.36 (-0.61, -0.11) |

Data are shown as median difference (95% credible interval). Cells highlighted in green show comparisons that significantly favour tirzepatide (dose according to column header).

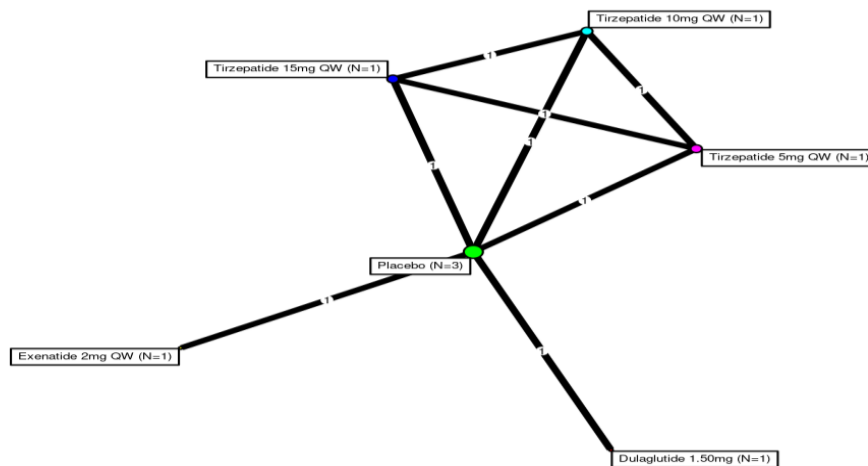
QW Once weekly.

### Change from Baseline in High-Density Lipoprotein Cholesterol

Three trials reported change from baseline in high-density lipoprotein (HDL) cholesterol to Week 40 (tirzepatide) and Week 26 ( $\pm$  4 weeks) (comparators) (**Figures S5.2.3 and S5.2.4; Table S5.2.2**).

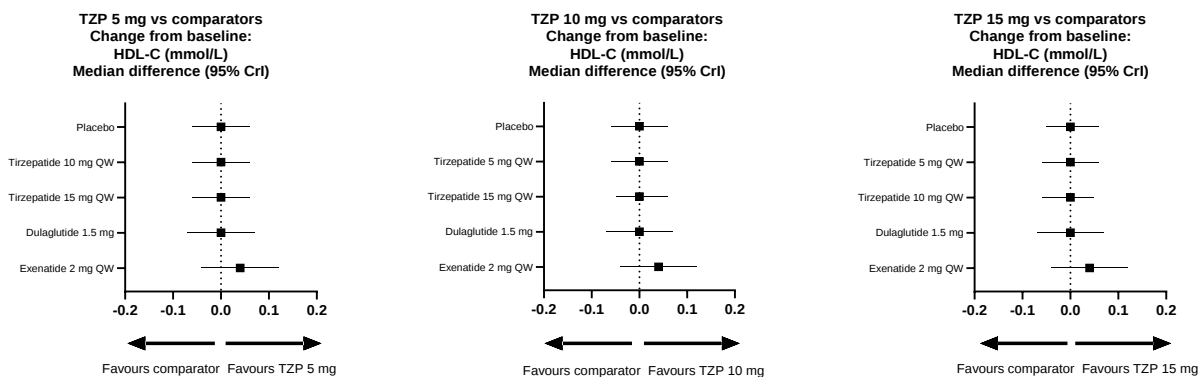
Tirzepatide 5, 10, and 15 mg showed no significant difference in HDL cholesterol from baseline compared with placebo, dulaglutide 1.50 mg, and exenatide 2 mg.

**Figure S5.2.3** Main analysis network for change from baseline in high-density lipoprotein cholesterol



QW Once weekly.

**Figure S5.2.4** Forest plots of change from baseline in high-density lipoprotein cholesterol (mmol/L) to Week 40 (TZP) and Week 26 ( $\pm 4$  weeks) (comparators)



CrI Credible interval, HDL-C High-density lipoprotein cholesterol, QW Once weekly, TZP Tirzepatide.

**Table S5.2.2** Change from baseline in high-density lipoprotein cholesterol (mmol/L) to Week 40 (tirzepatide) versus Week 26 ( $\pm 4$  weeks) (comparators)

| Comparator           | Tirzepatide 5 mg   | Tirzepatide 10 mg  | Tirzepatide 15 mg  |
|----------------------|--------------------|--------------------|--------------------|
| Placebo              | 0.00 (-0.06, 0.06) | 0.00 (-0.06, 0.06) | 0.00 (-0.05, 0.06) |
| Tirzepatide 5 mg QW  | —                  | 0.00 (-0.06, 0.06) | 0.00 (-0.06, 0.06) |
| Tirzepatide 10 mg QW | 0.00 (-0.06, 0.06) | —                  | 0.00 (-0.06, 0.05) |
| Tirzepatide 15 mg QW | 0.00 (-0.06, 0.06) | 0.00 (-0.05, 0.06) | —                  |
| Dulaglutide 1.50 mg  | 0.00 (-0.07, 0.07) | 0.00 (-0.07, 0.07) | 0.00 (-0.07, 0.07) |
| Exenatide 2 mg QW    | 0.04 (-0.04, 0.12) | 0.04 (-0.04, 0.12) | 0.04 (-0.04, 0.12) |

Data are shown as median difference (95% credible interval).

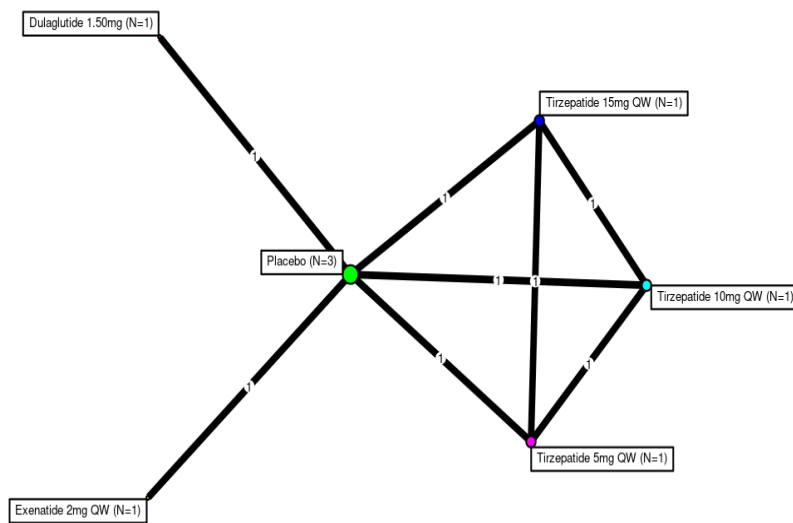
QW Once weekly.

### 5.3 Triglycerides

#### *Change from Baseline in Triglycerides*

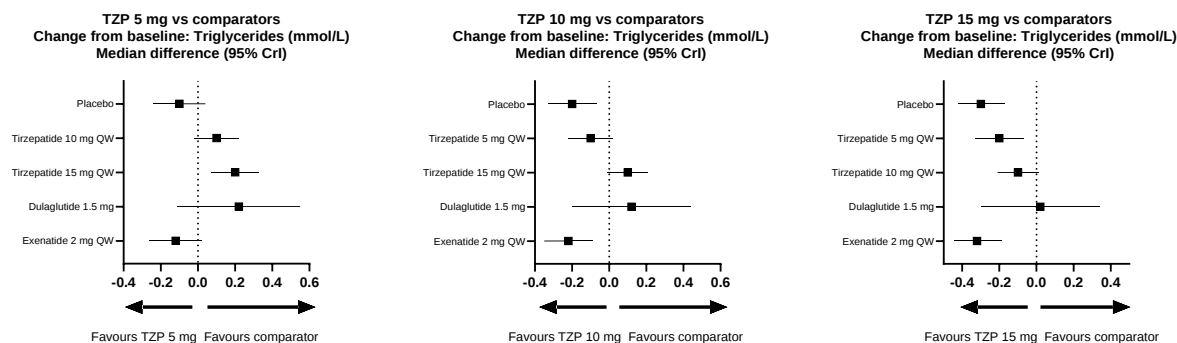
Three trials reported change from baseline in triglycerides to Week 40 (tirzepatide) and Week 26 ( $\pm 4$  weeks) (comparators) (**Figures S5.3.1 and S5.3.2; Table S5.3.1**). Tirzepatide 5 mg showed no significant changes in triglycerides from baseline compared with placebo, dulaglutide 1.50 mg, and exenatide 2 mg. Tirzepatide 10 mg showed significantly greater reductions in triglycerides from baseline compared with placebo and exenatide 2 mg. No significant difference was observed between tirzepatide 10 mg and dulaglutide 1.5 mg. Tirzepatide 15 mg showed significantly greater reductions in triglycerides from baseline compared with placebo and exenatide 2 mg. No significant difference was observed between tirzepatide 15 mg and dulaglutide 1.50 mg.

**Figure S5.3.1** Main analysis network for change from baseline in triglycerides



QW Once weekly.

**Figure S5.3.2** Forest plots of change from baseline in triglycerides (mmol/L) from baseline to Week 40 (TZP) and Week 26 ( $\pm 4$  weeks) (comparators)



CrI Credible interval, QW Once weekly, TZP Tirzepatide.

**Table S5.3.1** Change from baseline in triglycerides (mmol/L) to Week 40 (tirzepatide) versus Week 26 ( $\pm 4$  weeks) (comparators)

| Comparator           | Tirzepatide 5 mg    | Tirzepatide 10 mg    | Tirzepatide 15 mg    |
|----------------------|---------------------|----------------------|----------------------|
| Placebo              | -0.10 (-0.24, 0.04) | -0.20 (-0.33, -0.07) | -0.30 (-0.42, -0.17) |
| Tirzepatide 5 mg QW  | —                   | -0.10 (-0.22, 0.02)  | -0.20 (-0.33, -0.07) |
| Tirzepatide 10 mg QW | 0.10 (-0.02, 0.22)  | —                    | -0.10 (-0.21, 0.01)  |
| Tirzepatide 15 mg QW | 0.20 (0.07, 0.33)   | 0.10 (-0.01, 0.21)   | —                    |
| Dulaglutide 1.50 mg  | 0.22 (-0.11, 0.55)  | 0.12 (-0.20, 0.44)   | 0.02 (-0.30, 0.34)   |
| Exenatide 2 mg QW    | -0.12 (-0.26, 0.02) | -0.22 (-0.35, -0.09) | -0.32 (-0.44, -0.19) |

Data are shown as median difference (95% credible interval). Cells highlighted in green show comparisons that significantly favour tirzepatide (dose according to column header). Cells highlighted in red show comparisons that favour other tirzepatide doses or active treatments.

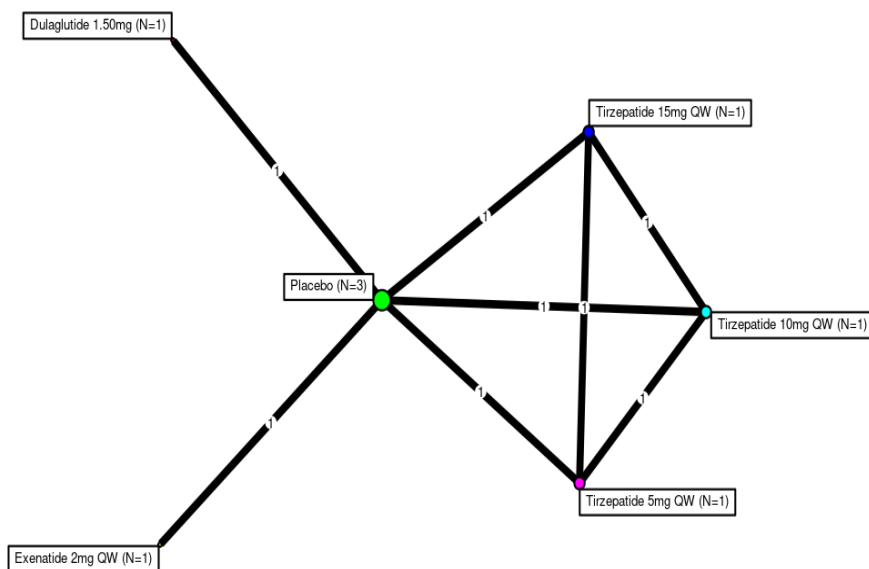
QW Once weekly.

## 5.4 Total Cholesterol

### Change from Baseline in Total Cholesterol

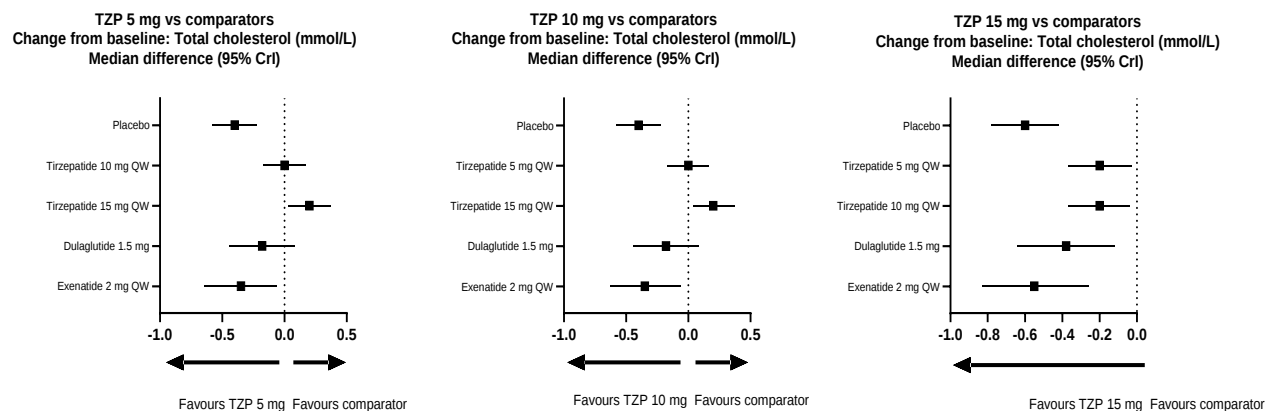
Three trials reported change from baseline in total cholesterol to Week 40 (tirzepatide) and Week 26 ( $\pm 4$  weeks) (comparators) (Figures S5.4.1 and S5.4.2; Table S5.41). Tirzepatide 5 and 10 mg showed significantly greater reductions in total cholesterol from baseline compared with placebo and exenatide 2 mg. No significant differences were observed with tirzepatide 5 and 10 mg compared with dulaglutide 1.50 mg. Tirzepatide 15 mg showed significantly greater reductions in total cholesterol from baseline compared with placebo, dulaglutide 1.50 mg, and exenatide 2 mg.

**Figure S5.4.1** Main analysis network for change from baseline in total cholesterol



QW Once weekly.

**Figure S5.4.2** Forest plots of change from baseline in total cholesterol (mmol/L) to Week 40 (TZP) and Week 26 ( $\pm 4$  weeks) (comparators)



CrI Credible interval, QW Once weekly, TZP Tirzepatide.

**Table S5.4.1** Change from baseline in total cholesterol (mmol/L) to Week 40 (tirzepatide) versus Week 26 ( $\pm 4$  weeks) (comparators)

| Comparator           | Tirzepatide 5 mg     | Tirzepatide 10 mg    | Tirzepatide 15 mg    |
|----------------------|----------------------|----------------------|----------------------|
| Placebo              | -0.40 (-0.58, -0.22) | -0.40 (-0.58, -0.22) | -0.60 (-0.78, -0.42) |
| Tirzepatide 5 mg QW  | —                    | 0.00 (-0.17, 0.17)   | -0.20 (-0.37, -0.03) |
| Tirzepatide 10 mg QW | 0.00 (-0.17, 0.17)   | —                    | -0.20 (-0.37, -0.04) |
| Tirzepatide 15 mg QW | 0.20 (0.03, 0.37)    | 0.20 (0.04, 0.37)    | —                    |
| Dulaglutide 1.50 mg  | -0.18 (-0.44, 0.08)  | -0.18 (-0.44, 0.08)  | -0.38 (-0.64, -0.12) |
| Exenatide 2 mg QW    | -0.35 (-0.64, -0.06) | -0.35 (-0.63, -0.06) | -0.55 (-0.83, -0.26) |

Data are shown as median difference (95% credible interval). Cells highlighted in green show comparisons that significantly favour tirzepatide (dose according to column header). Cells highlighted in red show comparisons that favour other tirzepatide doses or active treatments.

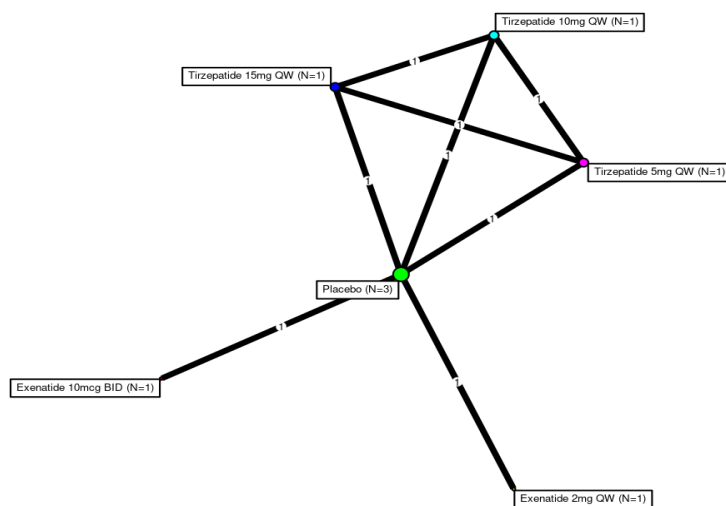
QW Once weekly.

## 5.5 Blood Pressure

### *Change from Baseline in Systolic Blood Pressure*

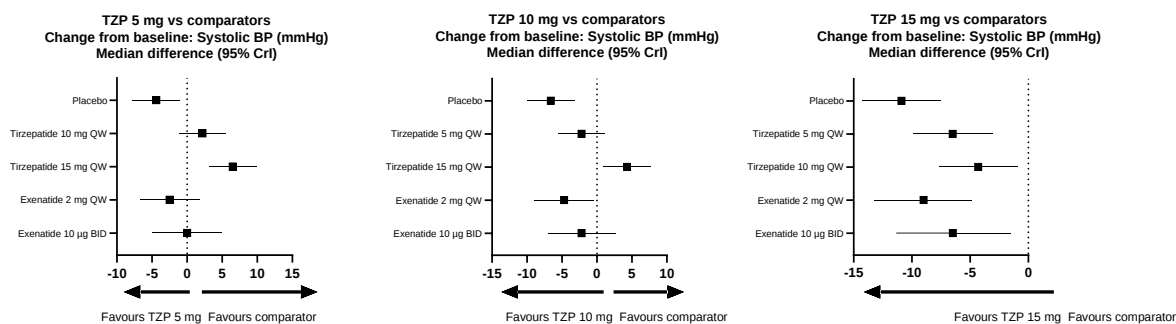
Three trials reported change from baseline in systolic blood pressure (SBP) to Week 40 (tirzepatide) and Week 26 ( $\pm 4$  weeks) (comparators) (**Figures S5.5.1 and S5.5.2; Table S5.5.1**). Tirzepatide 5 mg showed a significantly greater reduction in SBP from baseline compared with placebo. No significant differences were observed with tirzepatide 5 mg compared with exenatide 2 mg and exenatide 10 mcg. Tirzepatide 10 mg showed significantly greater reductions in SBP from baseline compared with placebo and exenatide 2 mg. No significant difference was observed between tirzepatide 10 mg and exenatide 10 mcg. Tirzepatide 15 mg showed significantly greater reductions in SBP from baseline compared with placebo, exenatide 2 mg, and exenatide 10 mcg.

**Figure S5.5.1** Main analysis network for change from baseline in systolic blood pressure



*BID* Twice daily, *QW* Once weekly.

**Figure S5.5.2** Forest plots of change from baseline in systolic blood pressure (mmHg) to Week 40 (TZP) and Week 26 ( $\pm 4$  weeks) (comparators)



*BID* Twice daily, *BP* Blood pressure, *CrI* Credible interval, *QW* Once weekly, *TZP* Tirzepatide.

**Table S5.5.1** Change from baseline in systolic blood pressure (mmHg) to Week 40 (tirzepatide) versus Week 26 ( $\pm$  4 weeks) (comparators)

| Comparator           | Tirzepatide 5 mg     | Tirzepatide 10 mg    | Tirzepatide 15 mg      |
|----------------------|----------------------|----------------------|------------------------|
| Placebo              | -4.38 (-7.82, -0.98) | -6.59 (-9.95, -3.24) | -10.89 (-14.24, -7.51) |
| Tirzepatide 5 mg QW  | —                    | -2.19 (-5.59, 1.18)  | -6.50 (-9.92, -3.10)   |
| Tirzepatide 10 mg QW | 2.19 (-1.18, 5.59)   | —                    | -4.31 (-7.67, -0.95)   |
| Tirzepatide 15 mg QW | 6.50 (3.1, 9.92)     | 4.31 (0.95, 7.67)    | —                      |
| Exenatide 2 mg QW    | -2.50 (-6.74, 1.75)  | -4.69 (-8.90, -0.50) | -8.99 (-13.24, -4.80)  |
| Exenatide 10 mcg BID | 0.01 (-4.90, 4.99)   | -2.19 (-7.05, 2.77)  | -6.48 (-11.35, -1.54)  |

Data are shown as median difference (95% credible interval). Cells highlighted in green show comparisons that significantly favour tirzepatide (dose according to column header). Cells highlighted in red show comparisons that favour other tirzepatide doses or active treatments.

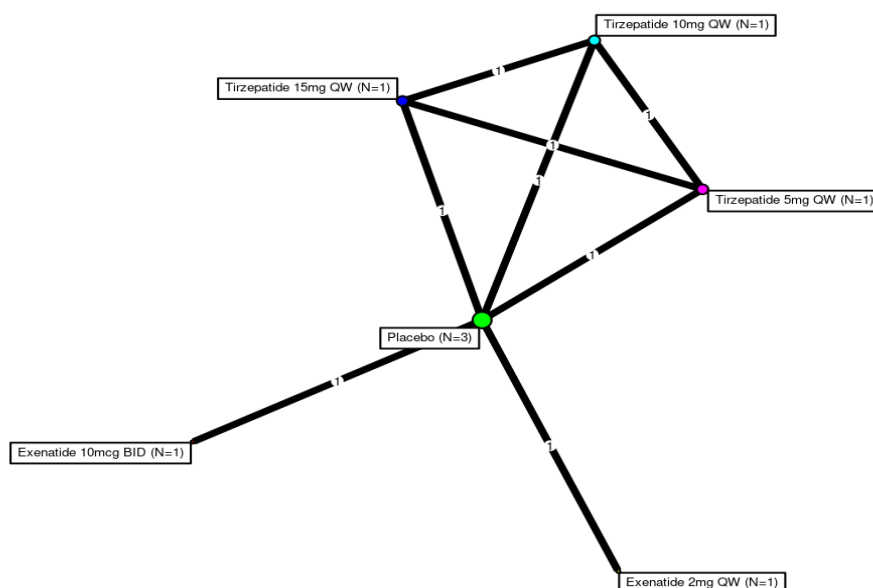
*BID* Twice daily, *QW* Once weekly.

#### *Change from Baseline in Diastolic Blood Pressure*

Three trials reported change from baseline in diastolic blood pressure (DBP) to Week 40 (tirzepatide) and Week 26 ( $\pm$  4 weeks) (comparators) (**Figures S5.5.3 and S5.5.4; Table S5.5.2**). Tirzepatide 5 mg showed a statistically significantly smaller decrease in DBP from baseline compared with exenatide 10 mcg. No statistically significant differences were observed with tirzepatide 5 mg compared with placebo and exenatide 2 mg. Tirzepatide 10 mg showed no statistically significant differences in DBP from baseline compared with placebo, exenatide 2 mg and exenatide 10 mcg.

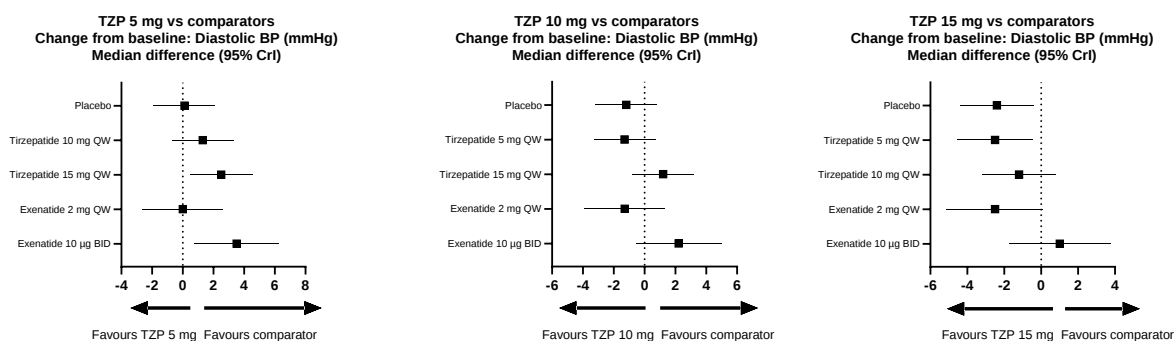
Tirzepatide 15 mg showed a statistically significantly greater reduction in DBP from baseline compared with placebo. No statistically significant differences were observed with tirzepatide 15 mg compared with exenatide 2 mg and exenatide 10 mcg.

**Figure S5.5.3** Main analysis network for change from baseline in diastolic blood pressure



*BID* Twice daily, *QW* Once weekly.

**Figure S5.5.4** Forest plots of change from baseline in diastolic blood pressure (mmHg) to Week 40 (TZP) and Week 26 ( $\pm 4$  weeks) (comparators)



*BID* Twice daily, *BP* Blood pressure, *CrI* Credible interval, *QW* Once weekly, *TZP* Tirzepatide.

**Table S5.5.2** Change from baseline in diastolic blood pressure (mmHg) to Week 40 (tirzepatide) versus Week 26 ( $\pm$  4 weeks) (comparators)

| Comparator           | Tirzepatide 5 mg   | Tirzepatide 10 mg   | Tirzepatide 15 mg    |
|----------------------|--------------------|---------------------|----------------------|
| Placebo              | 0.11 (−1.91, 2.11) | −1.19 (−3.18, 0.78) | −2.40 (−4.37, −0.40) |
| Tirzepatide 5 mg QW  | —                  | −1.30 (−3.31, 0.70) | −2.50 (−4.53, −0.49) |
| Tirzepatide 10 mg QW | 1.30 (−0.70, 3.31) | —                   | −1.20 (−3.20, 0.79)  |
| Tirzepatide 15 mg QW | 2.50 (0.49, 4.53)  | 1.20 (−0.79, 3.20)  | —                    |
| Exenatide 2 mg QW    | 0.00 (−2.61, 2.61) | −1.29 (−3.90, 1.30) | −2.50 (−5.13, 0.10)  |
| Exenatide 10 mcg BID | 3.51 (0.75, 6.29)  | 2.21 (−0.53, 4.98)  | 1.01 (−1.73, 3.79)   |

Data are shown as median difference (95% credible interval). Cells highlighted in green show comparisons that significantly favour tirzepatide (dose according to column header). Cells highlighted in red show comparisons that favour other tirzepatide doses or active treatments.

*BID* Twice daily, *QW* Once weekly.

## 6. Safety Matrix Tables

**Table S6.1** Likelihood of patients experiencing nausea (any grade permitted) at Week 40 (tirzepatide) versus Week 26 ( $\pm$  4 weeks) (comparators)

| Comparator           | Tirzepatide 5 mg   | Tirzepatide 10 mg  | Tirzepatide 15 mg  |
|----------------------|--------------------|--------------------|--------------------|
| Placebo              | 6.35 (1.95, 29.66) | 9.23 (2.96, 42.46) | 9.69 (3.11, 44.42) |
| Tirzepatide 5 mg QW  | —                  | 1.45 (0.71, 3.04)  | 1.53 (0.75, 3.17)  |
| Tirzepatide 10 mg QW | 0.69 (0.33, 1.40)  | —                  | 1.05 (0.54, 2.04)  |
| Tirzepatide 15 mg QW | 0.66 (0.32, 1.34)  | 0.95 (0.49, 1.86)  | —                  |
| Dulaglutide 1.50 mg  | 0.54 (0.06, 4.19)  | 0.78 (0.08, 5.93)  | 0.82 (0.09, 6.23)  |
| Exenatide 2 mg QW    | 4.73 (1.04, 27.36) | 6.89 (1.57, 39.15) | 7.24 (1.64, 40.87) |
| Exenatide 10 mcg BID | 0.80 (0.19, 4.31)  | 1.16 (0.29, 6.14)  | 1.22 (0.30, 6.43)  |
| Lixisenatide 20 mcg  | 1.19 (0.33, 5.94)  | 1.73 (0.50, 8.48)  | 1.82 (0.53, 8.88)  |

Data are shown as odds ratio (95% credible interval). Cells highlighted in red show comparisons that favour other tirzepatide doses or active treatments.

*BID* Twice daily, *QW* Once weekly.

**Table S6.2** Likelihood of patients experiencing vomiting (any grade permitted) at Week 40 (tirzepatide) versus Week 26 ( $\pm$  4 weeks) (comparators)

| Comparator           | Tirzepatide 5 mg     | Tirzepatide 10 mg    | Tirzepatide 15 mg     |
|----------------------|----------------------|----------------------|-----------------------|
| Placebo              | 3.11 (0.83, 15.49)   | 3.44 (0.97, 16.97)   | 6.10 (1.86, 28.34)    |
| Tirzepatide 5 mg QW  | —                    | 1.11 (0.41, 3.12)    | 1.97 (0.8, 5.08)      |
| Tirzepatide 10 mg QW | 0.90 (0.32, 2.45)    | —                    | 1.76 (0.75, 4.39)     |
| Tirzepatide 15 mg QW | 0.51 (0.20, 1.26)    | 0.57 (0.23, 1.34)    | —                     |
| Dulaglutide 1.50 mg  | 0.21 (0.01, 2.46)    | 0.23 (0.01, 2.07)    | 0.42 (0.01, 4.63)     |
| Exenatide 2 mg QW    | 13.44 (0.93, 603.82) | 14.84 (1.05, 664.81) | 26.28 (1.93, 1144.88) |
| Exenatide 10 mcg BID | 0.56 (0.10, 3.55)    | 0.62 (0.11, 3.88)    | 1.10 (0.21, 6.46)     |
| Lixisenatide 20 mcg  | 0.30 (0.05, 1.92)    | 0.33 (0.06, 2.11)    | 0.59 (0.11, 3.54)     |

Data are shown as odds ratio (95% credible interval). Cells highlighted in red show comparisons that favour other tirzepatide doses or active treatments.

*BID* Twice daily, *QW* Once weekly.

**Table S6.3** Likelihood of patients experiencing diarrhoea (any grade permitted) at Week 40 (tirzepatide) versus Week 26 ( $\pm$  4 weeks) (comparators)

| Comparator           | Tirzepatide 5 mg  | Tirzepatide 10 mg | Tirzepatide 15 mg |
|----------------------|-------------------|-------------------|-------------------|
| Placebo              | 1.25 (0.54, 2.87) | 1.31 (0.58, 2.99) | 2.41 (1.16, 5.24) |
| Tirzepatide 5 mg QW  | —                 | 1.05 (0.48, 2.32) | 1.93 (0.96, 4.03) |
| Tirzepatide 10 mg QW | 0.95 (0.43, 2.09) | —                 | 1.84 (0.92, 3.78) |
| Tirzepatide 15 mg QW | 0.52 (0.25, 1.04) | 0.54 (0.26, 1.09) | —                 |
| Dulaglutide 1.50 mg  | 0.39 (0.10, 1.36) | 0.41 (0.11, 1.42) | 0.76 (0.21, 2.52) |
| Exenatide 2 mg QW    | 0.89 (0.25, 3.10) | 0.93 (0.26, 3.22) | 1.73 (0.51, 5.77) |
| Exenatide 10 mcg BID | 0.48 (0.15, 1.51) | 0.51 (0.16, 1.58) | 0.94 (0.31, 2.81) |
| Lixisenatide 20 mcg  | 0.72 (0.25, 1.99) | 0.75 (0.27, 2.09) | 1.39 (0.53, 3.69) |

Data are shown as odds ratio (95% credible interval). Cells highlighted in red show comparisons that favour other tirzepatide doses or active treatments.

*BID* Twice daily, *QW* Once weekly.

**Table S6.4** Likelihood of patients with  $\geq 1$  episode of hypoglycaemia with BG <54 mg/dL (with or without severe hypoglycaemia) at Week 40 (tirzepatide) versus Week 26 ( $\pm$  4 weeks) (comparators)

| Comparator           | Tirzepatide 5 mg  | Tirzepatide 10 mg | Tirzepatide 15 mg |
|----------------------|-------------------|-------------------|-------------------|
| Placebo              | 1.29 (0.62, 2.74) | 1.69 (0.84, 3.50) | 1.16 (0.55, 2.48) |
| Tirzepatide 5 mg QW  | —                 | 1.31 (0.67, 2.61) | 0.9 (0.43, 1.85)  |
| Tirzepatide 10 mg QW | 0.76 (0.38, 1.50) | —                 | 0.69 (0.34, 1.36) |
| Tirzepatide 15 mg QW | 1.11 (0.54, 2.32) | 1.46 (0.74, 2.96) | —                 |
| Dulaglutide 1.50 mg  | 0.82 (0.30, 2.24) | 1.07 (0.40, 2.87) | 0.73 (0.27, 2.02) |
| Exenatide 2 mg QW    | 1.30 (0.44, 3.91) | 1.71 (0.58, 5.03) | 1.17 (0.39, 3.53) |
| Exenatide 10 mcg BID | 1.58 (0.62, 4.00) | 2.06 (0.84, 5.16) | 1.41 (0.55, 3.61) |
| Lixisenatide 20 mcg  | 0.81 (0.36, 1.84) | 1.06 (0.49, 2.36) | 0.73 (0.32, 1.66) |

Data are shown as odds ratio (95% credible interval).

*BG* Blood glucose, *BID* Twice daily, *QW* Once weekly.

**Table S6.5** Likelihood of patients with treatment discontinuation due to adverse events at Week 40 (tirzepatide) versus Week 26 ( $\pm$  4 weeks) (comparators)

| Comparator           | Tirzepatide 5 mg   | Tirzepatide 10 mg  | Tirzepatide 15 mg  |
|----------------------|--------------------|--------------------|--------------------|
| Placebo              | 2.68 (0.69, 13.39) | 3.88 (1.12, 18.82) | 5.18 (1.56, 24.34) |
| Tirzepatide 5 mg QW  | —                  | 1.45 (0.53, 4.2)   | 1.94 (0.75, 5.4)   |
| Tirzepatide 10 mg QW | 0.69 (0.24, 1.88)  | —                  | 1.33 (0.56, 3.25)  |
| Tirzepatide 15 mg QW | 0.52 (0.19, 1.34)  | 0.75 (0.31, 1.79)  | —                  |
| Dulaglutide 1.50 mg  | 0.77 (0.07, 7.13)  | 1.12 (0.1, 9.89)   | 1.51 (0.14, 13.28) |
| Exenatide 2 mg QW    | 1.48 (0.21, 11.24) | 2.17 (0.33, 15.49) | 2.9 (0.45, 20.11)  |
| Exenatide 10 mcg BID | 0.14 (0.00, 1.74)  | 0.21 (0.01, 2.42)  | 0.28 (0.01, 3.16)  |
| Lixisenatide 20 mcg  | 1.3 (0.29, 7.24)   | 1.89 (0.46, 10.09) | 2.54 (0.64, 13.18) |

Data are shown as odds ratio (95% credible interval). Cells highlighted in red show comparisons that favour other tirzepatide doses or active treatments.

*BID* Twice daily, *QW* Once weekly.