National Institute for Health and Care Excellence

Diabetes (type 1 and 2) in children and young people: diagnosis and management

[D] Evidence review for glucose-lowering agents for managing blood glucose levels in children and young people with type 2 diabetes

NICE guideline NG18

Evidence reviews underpinning recommendations 1.3.1 to 1.3.5, 1.3.23 to 1.3.29, and 1.3.38 to 1.3.61 and research recommendations in the NICE guideline.

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Guideline version (Final)

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1.1 Review question

In children and young people with type 2 diabetes, what is the clinical and cost effectiveness of glucose-lowering agents for improving glycaemic control in combination with metformin, and as an alternative when metformin is not tolerated or glucose levels are no longer optimally controlled?

1.1.1 Introduction

Since 2015, metformin has been the only drug in the UK licensed for use in children and young people with type 2 diabetes to manage blood glucose levels. It has become the standard treatment for children and young people who are not able to maintain glycaemic control – an HbA1c level of 48 mmol/mol (6.5%) or lower - through lifestyle changes such as diet and exercise. However, given the (until recently) minimal number of licensed drugs in the UK for use in children and young people, the use of drugs 'off label' – either as alternatives to metformin or when combined with it - is common due to a loss of glycaemic control (a result of a decline in *β*-cell function and severe insulin resistance) in those on metformin monotherapy. Several other glucose-lowering agents – in particular, liraglutide and exenatide (both GLP-1 receptor agonists), dapagliflozin (an SGLT2 inhibitor), and various insulin regimens - have been recently approved in the UK for use in a paediatric population. This review thus seeks to update recommendations regarding the use of metformin as mono- or combination therapy to effectively manage blood glucose in children and young people with type 2 diabetes.

1.1.2 Summary of the protocol

Table 1: PICO inclusion criteria

Population	Children and young people (people aged 18 years and under) with type 2 diabetes
Interventions	Glucose-lowering agents in the following classes of interventions will be considered either in combination with metformin or on their own as second line treatment when metformin is not tolerated or when diabetes is not optimally controlled: • DPP-4 inhibitors

	• GLP-1 receptor agonists • Insulin regimen • Meglitinides • SGLT2 inhibitors • Sulfonylureas • Thiazolidinediones
Comparator	**Second-line treatment** Any other combination of listed intervention + or – placebo • Placebo/Usual care **Metformin combination therapy** • Metformin monotherapy • Metformin + any other combination of listed interventions + or – placebo • Metformin + placebo
Outcomes	**Critical** • Glycated haemoglobin (HbA1c) • Glucose level • Change from baseline in BMI *z*-score • Participants needing rescue medication in form of insulin • Remission of Type 2 Diabetes **Important** • Serious adverse events: Diabetic Ketoacidosis/Hyperosmolar Hyperglycaemic State; Severe hypoglycaemic episode; Pancreatitis • Other gastrointestinal symptoms (abdominal discomfort, diarrhoea, nausea, vomiting) • Effects on co-morbidities • Quality of life

	• Mental health outcomes (including diabetes distress)
Study type	Phase 3 and Phase 4 Randomised Controlled Trials

For the full protocol see appendix A.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods section in appendix L.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.3.1 Search methods

The searches for the effectiveness evidence were run on 05 09 2022 to 06 09 2022 and the MEDLINE ALL search was updated on 27 02 2023. The following databases were searched: MEDLINE ALL (Ovid), Embase (Ovid), Cochrane Database of Systematic Reviews - CDSR (Wiley), Cochrane Central Register of Controlled Trials - CENTRAL (Wiley), and Epistemonikos (Epistemonikos Foundation). Full search strategies for each database are provided in Appendix B.

The searches for the cost effectiveness evidence were run on 08 09 2022 to 09 09 2022 and the MEDLINE ALL search was updated on 27 ow 2023. The following databases were searched: MEDLINE ALL (Ovid), Embase (Ovid), EconLit (Ovid), Economic Evaluations Database – EED (Centre for Reviews and Dissemination), Health Technology Assessment database - HTA (Centre for Reviews and Dissemination), and INAHTA database (INAHTA). Full search strategies for each database are provided in Appendix B.

A NICE information specialist conducted the searches. The MEDLINE strategy was quality assured by a trained NICE information specialist and all translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2016 PRESS Checklist.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

A systematic search carried out to identify potentially relevant studies found 5,894 references (see appendix B for the literature search strategy).

After de-duplication, 4,110 references were screened at title and abstract level against the review protocol, with 4,092 excluded at this level. Ten percent of references were screened separately by two reviewers with 100% agreement.

The full texts of 18 articles were ordered for closer inspection. Eight Phase 3 RCTs, all of which were international multisite trials, met the criteria specified in the review protocol (appendix A): 6 of these were double-blinded trials, 1 was a double-blind trial followed by an open-label extension period, and 1 was an open-label trial. Seven of the trials were two-arm trials, whilst one trial was a three arm trial comparing two active treatments with placebo. Evidence for the following 6 comparisons was identified:

Second-line treatment

- DPP-4 inhibitor vs Placebo then Metformin
    - Oral sitagliptin 100 mg per day (1 RCT)

Metformin combination therapy

- GLP-1 receptor agonist vs Placebo
    - Subcutaneous dulaglutide 0.75 mg or 1.5 mg per week (1 RCT)
    - Subcutaneous exenatide 2 mg per week (1 RCT)
    - Subcutaneous liraglutide ≤1.8 mg per day (1 RCT)
- Long-acting insulin regimen vs Intermediate-acting insulin regimen
    - Insulin detemir 100 or 200 U/mL per day vs Neutral protamine Hagedorn (isophane) insulin 100 or 200 IU/mL per day (1 RCT)
- SGLT2 inhibitor vs Placebo
    - Oral dapagliflozin 10 mg per week (1 RCT)
    - Oral empagliflozin 10 mg or 25 mg per day (1 3-arm RCT)
- DPP-4 inhibitor vs Placebo
    - Oral linagliptin 5 mg per day (1 3-arm RCT)
- DPP-4 inhibitor/Metformin fixed-dose combination vs Metformin
    - Oral sitagliptin 100 mg per day (1 RCT)

No Phase 4 trials were identified. No evidence was identified that examined drugs - either as second-line treatments as alternatives to metformin or when combined with metformin - in the following classes: meglitinides, sulfonylureas, and thiazolidinediones. No additional evidence was identified that examined the use of other insulin regimens to effectively manage blood glucose levels.

For a summary of the 8 included studies see Table 2. The clinical evidence study selection is presented as a PRISMA diagram in appendix C.

See section 1.1.14 References – included studies for the full references of the included studies.

1.1.4.2 Excluded studies

Details of studies excluded at full text, along with reasons for exclusion are given in appendix J.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2: Summary of included effectiveness studies

Study	Duration of trial and study type	Population	Intervention class Drug	Comparator	Outcomes
Arslanian 2022 (AWARD-PEDS trial)	26-week Phase 3 double-blind RCT[1]	• Aged 10 to <18 years with T2DM • HbA1c >6.5-9% if on diet and exercise or >6.5-11% if on metformin • Weight≥50kg • BMI>85th percentile (age- and sex-matched population as reference) • Stable metformin dose for 8 weeks	**GLP-1 receptor agonist** Subcutaneous dulaglutide injection 0.75 mg or 1.5 mg per week	**Placebo**	**Short term (≤26 weeks)** • HbA1c • Glucose level • BMI *z*-score • Participants needing rescue medication in form of insulin • Serious adverse events • Severe hypoglycaemic episode • Pancreatitis • Other gastrointestinal symptoms
Jalaludin 2022	54-week Phase 3 double-blind RCT[2]	• Aged 10-17 years with T2DM • HbA1c 6.5-10% if on ≥1500 mg/day metformin for ≥12 weeks or 7-10% if on metformin and insulin ≥12 weeks	**DPP-4 inhibitor/Metformin FDC + Placebo to Metformin** Oral sitagliptin 100 mg per day/Metformin FDC and matching placebo to oral metformin	**GLP-1 receptor agonist + Placebo to DPP-4 inhibitor/Metformin FDC** Oral metformin and matching placebo for oral sitagliptin 100 mg per day/Metformin FDC	**Short term (≤26 weeks) and long term (>26 weeks)** • HbA1c • Glucose level • BMI • Participants needing rescue medication in form of insulin

Study	Duration of trial and study type	Population	Intervention class Drug	Comparator	Outcomes
		• BMI≥85th percentile or history of being overweight or obese at T2DM diagnosis • Fasting C-peptide >0.6 ng/mL if on insulin or had T2DM<1 year, and FPG<13.3 mmol/L at randomisation			• Serious adverse events • Severe hypoglycaemic episode • Other gastrointestinal symptoms
Laffel 2023	52-week (first 26 weeks compared to placebo) Phase 3 double-blind RCT	• Aged 10-17 years with T2DM • HbA1c 6.5-10% at screening • BMI≥85th percentile	**DPP-4 inhibitor** Oral linagliptin 5 mg per day for 52 weeks **SGLT2 inhibitor** Oral empagliflozin 10 mg for 14 weeks then either 10 mg or 25 mg for 38 weeks (total 52 weeks)	**Placebo then DPP-4 inhibitor or SGLT2 inhibitor** Matching placebo for 26 weeks then either oral empagliflozin 10 mg or 25 mg, or oral linagliptin 5mg for 26 weeks	**Short-term (≤26 weeks)** • HbA1c • Glucose level • Weight • Participants needing rescue medication in form of insulin • Severe adverse events • Severe hypoglycaemic episode • Other gastrointestinal symptoms
Shankar 2022	54-week Phase 3	• Aged 10-17 years with T2DM	**DPP-4 inhibitor** Oral sitagliptin 100 mg per day	**Placebo then GLP-1 receptor agonist**	**Short term (≤26 weeks)** • HbA1c

Study	Duration of trial and study type	Population	Intervention class Drug	Comparator	Outcomes
	double-blind RCT[3]	• HbA1c 7-10% if on insulin, otherwise 6.5-10% • BMI≥85th percentile or history of being overweight or obese at T2DM diagnosis • Fasting C-peptide >0.6 ng/mL, and FPG<13.3 mmol/L at randomisation		Matching placebo for 20 weeks then oral metformin 1000 mg per day for 34 weeks	• Glucose level • Severe hypoglycaemic episode • Other gastrointestinal symptoms **Long term (>26 weeks)** • HbA1c • Glucose level • Serious adverse events • Severe hypoglycaemic episode • Other gastrointestinal symptoms
Tamborlane 2019 (ELLIPSE trial)	52-week Phase 3 RCT (26 weeks double blind then 26 weeks open-label)	• Aged 10-17 years with T2DM • HbA1c 7-11% if on diet and exercise or 6.5-11% if on metformin • BMI>85th percentile (age- and sex-	**GLP-1 receptor agonist** Subcutaneous liraglutide injection ≤1.8 mg per day	**Placebo** Matching placebo	**Short term (≤26 weeks)** • HbA1c • Glucose level • BMI *z*-score • Participants needing rescue medication in form of insulin **Long term (>26 weeks)**

Study	Duration of trial and study type	Population	Intervention class Drug	Comparator	Outcomes
		matched population as reference)			• HbA1c • Glucose level • BMI *z*-score • Participants needing rescue medication in form of insulin • Serious adverse events • Severe hypoglycaemic episode • Other gastrointestinal symptoms
Tamborlane, Bishai et al. 2022	24-week Phase 3 double-blind RCT[4]	• Aged 10 to <18 years with T2DM • HbA1c 6.5-12% if on insulin or sulfonylurea, otherwise 6.5-11%	**GLP-1 receptor agonist** Subcutaneous exenatide injection 2 mg per week	**Placebo** Matching placebo	**Short term (≤26 weeks)** • HbA1c • Glucose level • Participants needing rescue medication in form of insulin • Serious adverse events • Severe hypoglycaemic episode • Other gastrointestinal symptoms
Tamborlane, Laffal et al. 2022	24-week Phase 3	• Aged 10-24 years with T2DM	**SGLT2 inhibitor**	**Placebo** Matching placebo	**Short term (≤26 weeks)** • HbA1c

Study	Duration of trial and study type	Population	Intervention class Drug	Comparator	Outcomes
	double-blind RCT[5]	• HbA1c 6.5-11% • FPG≤14.2 mmol/L • Stable dose of metformin≥1000 mg/day for 8 weeks	Oral dapagliflozin 10 mg per week		• Glucose level • BMI *z*-score • Participants needing rescue medication in form of insulin • Serious adverse events • Diabetic Ketoacidosis/Hyperosmolar Hyperglycaemic State • Severe hypoglycaemic episode • Other gastrointestinal symptoms
Wheeler 2018	26-week Phase 3 open-label RCT[6]	• Aged 10-17 years with T2DM • HbA1c 7-10.5% • Insufficient glycaemic control with maximum-tolerated metformin dose	**Insulin regimen** Subcutaneous insulin detemir injection 100 or 200 U/mL per day	**Insulin regimen** Subcutaneous neutral protamine Hagedorn (NPH) insulin (also known as 'isophane insulin') 100 or 200 IU/mL per day	**Short term (≤26 weeks)** • HbA1c • Glucose level • BMI *z*-score • Participants needing rescue medication in form of insulin • Serious adverse events • Severe hypoglycaemic episode • Other gastrointestinal symptoms

Abbreviations: BMI, body mass index; DPP-4, dipeptidyl peptidase-4; FDC, fixed-dose combination; FPG, fasting plasma glucose; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; IU/mL, international units per millilitre; mg, milligram; mmol/L, millimoles per litre; ng/mL, nanograms per millilitre; U/ml, units per millilitre; SGLT2, Sodium-glucose co-transporter-2; T2DM, Type 2 diabetes mellitus.

Notes: 1, Trial had 3-arms but also reports pooled data, which is used in this review, for the dulaglutide 0.75 mg and 1.5 mg arms. Trial also included a subsequent 26-week open-label extension period in which all participants received dulaglutide; 2, Study reports combined results for two 54-week Phase 3 double-blind RCTs, comparing either twice-daily fixed-dose combination of sitagliptin 50 mg and immediate-release metformin added to placebo to immediate-release metformin, or once daily fixed-dose combination of sitagliptin 100 mg and extended-release metformin added to placebo to extended-release metformin; 3, Originally a 4-arm trial but two arms were discontinued. Sitagliptin arm comprised 54 weeks of sitagliptin 100 mg plus 1 tablet of matching placebo to metformin 500 mg prior to morning meal and 1 matching placebo to metformin 500 mg prior to evening meal. Placebo arm comprised 20 weeks of matching placebo to sitagliptin 100 mg plus 1 tablet matching placebo to metformin 500 mg prior to morning meal and 1 tablet of matching placebo to metformin 500 mg prior to evening meal. From weeks 20-54, participants received matching placebo to sitagliptin 100 mg and 2 tablets of metformin 500 mg prior to both morning and evening meal; 4, Trial also included a subsequent 28-week single-arm crossover open-label extension period to exenatide for participants in placebo group; 5, Trial also included a subsequent 28-week open-label extension period in which all participants received dapagliflozin. 6, Trial was terminated early due to problems recruiting participants.

See appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Second-line treatment

DPP-4 inhibitor vs Placebo then Metformin

Table 3: Summary of short- and long-term outcomes (≤26 weeks and >26 weeks) for DPP-4 inhibitor (Sitagliptin) vs Placebo then Metformin

Outcome	No. of participants (studies)	Effect (95% CI)	Certainty	Interpretation of effect
HbA1c % - change score ≤26 weeks	190 (1 RCT)	MD -0.3 (-0.77, 0.17)	LOW	Could not differentiate
HbA1c % - change score >26 weeks	185 (1 RCT)	**MD 0.6 (0.18, 1.02)**	LOW	**Favours Placebo then Metformin**

Outcome	No. of participants (studies)	Effect (95% CI)	Certainty	Interpretation of effect
HbA1c<7% - **≤26 weeks** (RR>1 favours GLP-1 receptor agonist)	190 (1 RCT)	RR 1.34 (0.96, 1.87)	LOW	Could not differentiate
HbA1c<7% **>26 weeks** (RR>1 favours GLP-1 receptor agonist)	190 (1 RCT)	RR 0.75 (0.50, 1.13)	LOW	Could not differentiate
FPG mmol/L – change score **≤26 weeks**	190 (1 RCT)	MD 0.08 (-0.81, 0.97)	MODERATE	Could not differentiate
FPG mmol/L – change score **>26 weeks**	185 (1 RCT)	MD 0.45 (-0.21, 1.11)	LOW	Could not differentiate

Outcome	No. of participants (studies)	Effect (95% CI)	Certainty	Interpretation of effect
Serious adverse events **>26 weeks**	190 (1 RCT)	RR 2.25 (0.72, 7.06)	VERY LOW	Could not differentiate
Severe hypoglycaemic episode **≤26 weeks** and **>26 weeks**	190 (1 RCT)	Not estimable	VERY LOW	Could not differentiate
Other gastrointestinal symptoms - Short term (≤26 weeks)				
Nausea	190 (1 RCT)	RR 5.0 (0.6, 42.0)	VERY LOW	Could not differentiate
Vomiting	190 (1 RCT)	RR 2.00 (0.38, 10.66)	VERY LOW	Could not differentiate

Outcome	No. of participants (studies)	Effect (95% CI)	Certainty	Interpretation of effect
Diarrhoea	190 (1 RCT)	RR 0.60 (0.15, 2.44)	VERY LOW	Could not differentiate
Abdominal discomfort	190 (1 RCT)	RR 0.89 (0.36, 2.21)	VERY LOW	Could not differentiate
Other gastrointestinal symptoms - Long term (>26 weeks)				
Nausea	190 (1 RCT)	RR 1.25 (0.35, 4.51)	VERY LOW	Could not differentiate
Vomiting	190 (1 RCT)	RR 0.86 (0.30, 2.46)	VERY LOW	Could not differentiate
Diarrhoea	190 (1 RCT)	RR 0.73 (0.31, 1.73)	VERY LOW	Could not differentiate

Outcome	No. of participants (studies)	Effect (95% CI)	Certainty	Interpretation of effect
Abdominal discomfort	190 (1 RCT)	RR 0.85 (0.40 1.79)	VERY LOW	Could not differentiate

Metformin combination therapy

GLP-1 receptor agonist vs Placebo

Table 4: Summary of short-term outcomes (≤26 weeks) for GLP-1 receptor agonist vs Placebo

Outcome	No. of participants (studies)	Effect (95% CI)	Certainty	Interpretation of effect
HbA1c % - change score	370 (3 RCTs)	**MD -1.14 (-1.48, -0.79)**	LOW	**Favours GLP-1 receptor agonist**
Dulaglutide	154 (1 RCT)	**MD -1.4 (-1.95, -0.85)**	LOW	**Favours GLP-1 receptor agonist**

Outcome	No. of participants (studies)	Effect (95% CI)	Certainty	Interpretation of effect
Exenatide	82 (1 RCT)	**MD -0.85 (-1.51, -0.19)**	VERY LOW	**Favours GLP-1 receptor agonist**
Liraglutide	134 (1 RCT)	**MD -1.06 (-1.66, -0.46)**	MODERATE	**Favours GLP-1 receptor agonist**
HbA1c≤6.5% - Overall (RR>1 favours GLP-1 agonist)	236 (2 RCTs)	**RR 4.24 (1.92, 9.37)**	LOW	**Favours GLP-1 receptor agonist**
Dulaglutide	154 (1 RCT)	**RR 4.26 (1.80, 10.09)**	LOW	**Favours GLP-1 receptor agonist**
Exenatide	82 (1 RCT)	RR 4.14 (0.56, 30.57)	VERY LOW	Could not differentiate
HbA1c<7% (RR>1 favours GLP-1 agonist)	370 (3 RCTs)	**RR 2.67 (1.25, 5.68)**	LOW	**Favours GLP-1 receptor agonist**

Outcome	No. of participants (studies)	Effect (95% CI)	Certainty	Interpretation of effect
Dulaglutide	154 (1 RCT)	**RR 3.75 (1.84, 7.65)**	LOW	**Favours GLP-1 receptor agonist**
Exenatide	82 (1 RCT)	RR 5.79 (0.81, 41.63)	VERY LOW	Could not differentiate
Liraglutide	134 (1 RCT)	**RR 1.73 (1.21, 2.48)**	LOW	**Favours GLP-1 receptor agonist**
FPG mmol/L – change score	370 (3 RCTs)	**MD -1.8 (-2.48, -1.11)**	LOW	**Favours GLP-1 receptor agonist**
Dulaglutide	154 (1 RCT)	**MD -2 (-3.0, -1.0)**	LOW	**Favours GLP-1 receptor agonist**
Exenatide	82 (1 RCT)	MD -1.2 (-2.72, 0.32)	LOW	Could not differentiate
Liraglutide	134 (1 RCT)	**MD -1.88 (-3.1, -0.66)**	HIGH	**Favours GLP-1 receptor agonist**

Outcome	No. of participants (studies)	Effect (95% CI)	Certainty	Interpretation of effect
BMI *z*-score – change score	288 (2 RCTs)	MD -0.05 (-0.15, 0.05)	LOW	Could not differentiate
Dulaglutide	154 (1 RCT)	MD -0.01 (-0.56, 0.54)	LOW	Could not differentiate
Liraglutide	134 (1 RCT)	MD -0.05 (-0.15, 0.05)	HIGH	Could not differentiate
Participants needing rescue medication in form of insulin	371 (3 RCTs)	**RR 0.35 (0.20, 0.63)**	LOW	**Favours GLP-1 receptor agonist**
Dulaglutide	154 (1 RCT)	**RR 0.17 (0.05, 0.58)**	LOW	**Favours GLP-1 receptor agonist**
Exenatide	82 (1 RCT)	RR 1.27 (0.05, 30.15)	VERY LOW	Could not differentiate

Outcome	No. of participants (studies)	Effect (95% CI)	Certainty	Interpretation of effect
Liraglutide	135 (1 RCT)	**RR 0.43 (0.21, 0.86)**	MODERATE	**Favours GLP-1 receptor agonist**
Serious adverse events	236 (2 RCTs)	RR 0.45 (0.11, 1.78)	VERY LOW	Could not differentiate
Dulaglutide	154 (1 RCT)	RR 0.33 (0.06, 1.91)	VERY LOW	Could not differentiate
Exenatide	82 (1 RCT)	RR 0.78 (0.07, 8.19)	VERY LOW	Could not differentiate
Severe hypoglycaemic episode	236 (2 RCTs)	RR 1.20 (0.05, 28.44)	VERY LOW	Could not differentiate
Dulaglutide	154 (1 RCT)	Not estimable	VERY LOW	Could not differentiate
Exenatide	82 (1 RCT)	RR 1.20 (0.05, 28.44)	VERY LOW	Could not differentiate

Outcome	No. of participants (studies)	Effect (95% CI)	Certainty	Interpretation of effect
Pancreatitis	154 (1 RCT)	Not estimable	VERY LOW	Could not differentiate
Other gastrointestinal symptoms				
Nausea	236 (2 RCTs)	RR 1.79 (0.70, 4.60)	VERY LOW	Could not differentiate
Vomiting	236 (2 RCTs)	RR 3.72 (1.03, 13.41)	VERY LOW	Could not differentiate
Diarrhoea	236 (2 RCTs)	RR 1.42 (0.67, 3.01)	VERY LOW	Could not differentiate
Abdominal discomfort	236 (2 RCTs)	RR 0.53 (0.19, 1.51)	VERY LOW	Could not differentiate

Table 5: Summary of long-term outcomes (>26 weeks) for GLP-1 agonist (Liraglutide) vs Placebo

Outcome	No of participants (studies)	Effect (95% CI)	Certainty	Interpretation of effect
HbA1c % - change score	134 (1 RCT)	**MD -1.3 (-1.90, -0.79)**	MODERATE	**Favours GLP-1 receptor agonist**
FPG mmol/L - change score	134 (1 RCT)	**MD -1.81 (-3.18, -0.44)**	MODERATE	**Favours GLP-1 receptor agonist**
BMI *z*-score - change score	134 (1 RCT)	**MD -0.18 (-0.34, -0.02)**	LOW	**Favours GLP-1 receptor agonist**
Participants needing rescue medication in form of insulin	135 (1 RCT)	**RR 0.58 (0.37, 0.92)**	LOW	**Favours GLP-1 receptor agonist**
Serious adverse events	134 (1 RCT)	RR 2.32 (0.75, 7.16)	VERY LOW	Could not differentiate
Severe hypoglycaemic episode	134 (1 RCT)	RR 0.34 (0.01, 8.28)	VERY LOW	Could not differentiate

Outcome	No of participants (studies)	Effect (95% CI)	Certainty	Interpretation of effect
Other gastrointestinal symptoms				
Nausea	134 (1 RCT)	**RR 2.18 (1.06, 4.46)**	LOW	**Favours Placebo**
Vomiting	134 (1 RCT)	**RR 2.92 (1.23, 6.95)**	LOW	**Favours Placebo**
Diarrhoea	134 (1 RCT)	RR 1.40 (0.70, 2.83)	VERY LOW	Could not differentiate
Abdominal discomfort	134 (1 RCT)	RR 2.06 (0.82, 5.17)	LOW	Could not differentiate

Long-acting insulin regimen vs Intermediate-acting insulin regimen

Table 6: Summary of short-term outcomes (≤26 weeks) for Long-acting insulin (detemir) regimen vs Intermediate-acting (NPH) insulin regimen

Outcome	No of participants (studies)	Effect (95% CI)	Certainty	Interpretation of effect
HbA1c % - post-intervention score	42 (1 RCT)	MD 0.17 (-0.75, 1.09)	VERY LOW	Could not differentiate
HbA1c<7% (RR>1 favours long-acting insulin regimen)	42 (1 RCT)	RR 0.79 (0.30, 2.08)	VERY LOW	Could not differentiate
FPG mmol/L - po	42 (1 RCT)	MD -0.2 (-1.87, 1.47)	VERY LOW	Could not differentiate
BMI *z*-score	42 (1 RCT)	MD 0.15 (-0.18, 0.48)	VERY LOW	Could not differentiate

Outcome	No of participants (studies)	Effect (95% CI)	Certainty	Interpretation of effect
Participants needing rescue medication in form of insulin	42 (1 RCT)	RR 3.29 (0.14, 76.33)	VERY LOW	Could not differentiate
Serious adverse events	42 (1 RCT)	RR 0.37 (0.02, 8.48)	VERY LOW	Could not differentiate
Severe hypoglycaemic episode	42 (1 RCT)	Not estimable	VERY LOW	Could not differentiate
Nocturnal severe hypoglycaemic episode	42 (1 RCT)	Not estimable	VERY LOW	Could not differentiate
Other gastrointestinal symptoms				
Vomiting	42 (1 RCT)	RR 1.10 (0.25, 4.84)	VERY LOW	Could not differentiate

SGLT2 inhibitor vs Placebo

Table 7: Summary of short-term outcomes (≤26 weeks) for SGLT2 inhibitor vs Placebo

Outcome	No. of participants (studies)	Effect (95% CI)	Certainty	Interpretation of effect
HbA1c % - change score	177 (2 RCTs)	MD -0.81 (-1.34, -0.28)	VERY LOW	**Favours SGLT2 inhibitor**
Dapagliflozin	72 (1 RCT)	MD -0.75 (-1.65, 0.15)	VERY LOW	Could not differentiate
Empagliflozin	105 (1 RCT)	MD -0.84 (-1.49, -0.19)	MODERATE	**Favours Empagliflozin**
HbA1c<6.5% Empagliflozin (RR>1 favours SGLT2 inhibitor)	105 (1 RCT)	RR 2.24 (0.84 to 6.01)	MODERATE	Could not differentiate

Outcome	No. of participants (studies)	Effect (95% CI)	Certainty	Interpretation of effect
Overall HbA1c<7% (RR>1 favours SGLT2 inhibitor)	177 (2 RCTs)	RR 1.25 (0.78, 1.99)	VERY LOW	Could not differentiate
Dapagliflozin	72 (1 RCT)	RR 1.03 (0.49, 2.19)	VERY LOW	Could not differentiate
Empagliflozin	105 (1 RCT)	RR 1.41(0.77, 2.58)	LOW	Could not differentiate
FPG mmol/L – change score	177 (2 RCTs)	MD -1.5 (-2.52, -0.48)	LOW	**Favours SGLT2 inhibitor**
Dapagliflozin	72 (1 RCT)	MD -0.78 (-2.41, 0.85)	LOW	Could not differentiate

Outcome	No. of participants (studies)	Effect (95% CI)	Certainty	Interpretation of effect
Empagliflozin	105 (1 RCT)	MD -1.95 (-3.25, -0.65)	HIGH	**Favours Empagliflozin**
BMI *z*-score - Dapagliflozin	72 (1 RCT)	MD 0.03 (-0.08, 0.14)	VERY LOW	Could not differentiate
Weight (kg) - Empagliflozin	104 (1 RCT)	MD -0.75 (-2.68, 1.18)	MODERATE	Could not differentiate
Participants needing rescue medication in form of insulin	177 (2 RCTs)	RR 0.75 (0.29, 1.91)	VERY LOW	Could not differentiate
Dapagliflozin	72 (1 RCT)	RR 0.56 (0.10, 3.18)	VERY LOW	Could not differentiate

Outcome	No. of participants (studies)	Effect (95% CI)	Certainty	Interpretation of effect
Empagliflozin	105 (1 RCT)	RR 0.85 (0.28, 2.61)	LOW	Could not differentiate
Serious adverse events - Overall	177 (2 RCTs)	RR 0.46 (0.09, 2.46)	VERY LOW	Could not differentiate
Dapagliflozin	72 (1 RCT)	RR 0.42 (0.04, 4.46)	VERY LOW	Could not differentiate
Empagliflozin	105 (1 RCT)	RR 0.51 (0.05, 5.45)	LOW	Could not differentiate
Diabetic ketoacidosis/ Hyperosmolar Hyperglycaemic State - Empagliflozin	105 (1 RCT)	RR 0.34 (0.01, 8.15)	LOW	Could not differentiate

Outcome	No. of participants (studies)	Effect (95% CI)	Certainty	Interpretation of effect
Severe hypoglycaemic episode - Dapagliflozin	72 (1 RCT)	RR 1.69 (0.16, 17.84)	VERY LOW	Could not differentiate
Pancreatitis - Empagliflozin	105 (1 RCT)	RR 0.34 (0.01, 8.15)	LOW	Could not differentiate
Other gastrointestinal symptoms				
Nausea - Overall	177 (2 RCTs)	RR 1.78 (0.49, 6.48)	LOW	Could not differentiate
Dapagliflozin	72 (1 RCT)	RR 5.95 (0.32, 111.17)	VERY LOW	Could not differentiate
Empagliflozin	105 (1 RCT)	RR 1.02 (0.22, 4.82)	LOW	Could not differentiate

Outcome	No. of participants (studies)	Effect (95% CI)	Certainty	Interpretation of effect
Vomiting - Overall	177 (2 RCTs)	RR 2.11 (0.48, 9.30)	LOW	Could not differentiate
Dapagliflozin	72 (1 RCT)	RR 4.25 (0.21, 85.51)	VERY LOW	Could not differentiate
Empagliflozin	105 (1 RCT)	RR 1.53 (0.27, 8.78)	LOW	Could not differentiate
Diarrhoea - Overall	177 (2 RCTs)	RR 0.54 (0.16, 1.81)	VERY LOW	Could not differentiate
Dapagliflozin	72 (1 RCT)	RR 0.85 (0.13, 5.68)	VERY LOW	Could not differentiate

Outcome	No. of participants (studies)	Effect (95% CI)	Certainty	Interpretation of effect
Empagliflozin	105 (1 RCT)	RR 0.41 (0.08, 2.01)	LOW	Could not differentiate
Abdominal discomfort - Empagliflozin	105 (1 RCT)	RR 0.76 (0.18, 3.25)	LOW	Could not differentiate

DPP-4 inhibitor vs Placebo

Table 8: Summary of short-term outcomes (≤26 weeks) for DPP-4 inhibitor (Linagliptin) vs Placebo

Outcome	No of participants (studies)	Effect (95% CI)	Certainty	Interpretation of effect
HbA1c % - change score	105 (1 RCT)	MD -0.34 (-0.98, 0.3)	MODERATE	Could not differentiate
HbA1c %<6.5% (RR>1 favours DPP-4 inhibitor)	105 (1 RCT)	RR 1.63 (0.57, 4.66)	LOW	Could not differentiate
HbA1c<7% (RR>1 favours DPP-4 inhibitor)	105 (1 RCT)	RR 1.10 (0.57, 2.10)	LOW	Could not differentiate
FPG mmol/L – change score	105 (1 RCT)	MD -0.3 (-1.58, 0.98)	HIGH	Could not differentiate
Weight (kg) – change score	105 (1 RCT)	MD 1.46 (-0.48, 3.4)	MODERATE	Could not differentiate

Outcome	No of participants (studies)	Effect (95% CI)	Certainty	Interpretation of effect
Participants needing rescue medication in form of insulin	105 (1 RCT)	RR 0.68 (0.20, 2.27)	LOW	Could not differentiate
Diabetic ketoacidosis/ Hyperosmolar Hyperglycaemic State	105 (1 RCT)	RR 0.34 (0.01, 8.15)	LOW	Could not differentiate
Serious adverse events	105 (1 RCT)	RR 1.02 (0.07, 15.87)	LOW	Could not differentiate
Pancreatitis	105 (1 RCT)	RR 0.34 (0.01, 8.15)	LOW	Could not differentiate
Other gastrointestinal symptoms				
Nausea	105 (1 RCT)	RR 1.02 (0.22, 4.82)	LOW	Could not differentiate

Outcome	No of participants (studies)	Effect (95% CI)	Certainty	Interpretation of effect
Vomiting	105 (1 RCT)	RR 2.55 (0.52, 12.55)	LOW	Could not differentiate
Diarrhoea	105 (1 RCT)	RR 0.61 (0.15, 2.43)	LOW	Could not differentiate
Abdominal discomfort	105 (1 RCT)	RR 1.02 (0.27, 3.86)	LOW	Could not differentiate

DPP-4 inhibitor/Metformin FDC vs Metformin

Table 8: Summary of short- and long-term outcomes (≤26 weeks and >26 weeks) for DPP-4 inhibitor (Sitagliptin)/Metformin FDC vs Metformin

Outcome	No of participants (studies)	Effect (95% CI)	Certainty	Interpretation of effect
HbA1c % - post-intervention score **≤26 weeks**	220 (1 RCT)	MD -0.2 (-0.57, 0.17)	LOW	Could not differentiate
HbA1c % - post-intervention score **≤26 weeks**	147 (1 RCT)	MD 0.3 (-0.43, 1.03)	LOW	Could not differentiate
HbA1c<7% **≤26 weeks** (RR>1 favours DPP-4 inhibitor /Metformin)	220 (1 RCT)	RR 1.39 (0.98, 1.97)	LOW	Could not differentiate

Outcome	No of participants (studies)	Effect (95% CI)	Certainty	Interpretation of effect
HbA1c<7% **>26 weeks** (RR>1 favours DPP-4 inhibitor /Metformin)	147 (1 RCT)	RR 1.15 (0.70, 1.91)	VERY LOW	Could not differentiate
FPG mmol/L - post-intervention score **≤26 weeks**	220 (1 RCT)	MD -0.82 (-1.66, 0.02)	LOW	Could not differentiate
FPG mmol/L - post-intervention score **>26 weeks**	147 (1 RCT)	MD 0.34 (-0.75, 1.43)	LOW	Could not differentiate
BMI (kg/m2) - post-intervention score **Short term**	220 (1 RCT)	MD -0.2 (-0.64, 0.24)	LOW	Could not differentiate

Outcome	No of participants (studies)	Effect (95% CI)	Certainty	Interpretation of effect
BMI (kg/m2) - post-intervention score **>26 weeks**	147 (1 RCT)	MD 0.3 (-0.48, 1.08)	LOW	Could not differentiate
Participants needing rescue medication in form of insulin **≤26 weeks**	220 (1 RCT)	RR 0.22 (0.08, 0.63)	MODERATE	Could not differentiate
Participants needing rescue medication in form of insulin **>26 weeks**	147 (1 RCT)	RR 0.70 (0.43, 1.12)	LOW	Could not differentiate
Serious adverse events **≤26 weeks**	220 (1 RCT)	RR 1.76 (0.43, 7.19)	VERY LOW	Could not differentiate

Outcome	No of participants (studies)	Effect (95% CI)	Certainty	Interpretation of effect
Serious adverse events **>26 weeks**	147 (1 RCT)	RR 1.38 (0.38, 4.92)	VERY LOW	Could not differentiate
Severe hypoglycaemic episode **≤26 weeks**	220 (1 RCT)	1. RR 0.79 (0.18, 3.46)	VERY LOW	Could not differentiate
Severe hypoglycaemic episode **>26 weeks**	147 (1 RCT)	RR 1.10 (0.16, 7.60)	VERY LOW	Could not differentiate
Other gastrointestinal symptoms – Short term (≤26 weeks)				
Nausea	220 (1 RCT)	RR 0.75 (0.25, 2.30)	VERY LOW	Could not differentiate
Vomiting	220 (1 RCT)	RR 1.06 (0.27, 4.12)	VERY LOW	Could not differentiate

Outcome	No of participants (studies)	Effect (95% CI)	Certainty	Interpretation of effect
Diarrhoea	220 (1 RCT)	RR 1.90 (0.66, 5.49)	VERY LOW	Could not differentiate
Abdominal discomfort	220 (1 RCT)	RR 0.38 (0.14, 1.01)	VERY LOW	Could not differentiate
Other gastrointestinal symptoms – Long term (>26 weeks)				
Nausea	147 (1 RCT)	RR 1.83 (0.45, 7.39)	VERY LOW	Could not differentiate
Vomiting	147 (1 RCT)	RR 1.10 (0.16, 7.39)	VERY LOW	Could not differentiate
Diarrhoea	147 (1 RCT)	RR 0.73 (0.22, 2.49)	VERY LOW	Could not differentiate

Outcome	No of participants (studies)	Effect (95% CI)	Certainty	Interpretation of effect
Abdominal discomfort	147 (1 RCT)	RR 0.79 (0.26, 2.36)	VERY LOW	Could not differentiate

See appendix F for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

A search was performed to identify published economic evaluations of relevance, this search retrieved 1996 studies. Based on title and abstract screening 1986 studies were excluded. After full text screening 10 studies were excluded (see Appendix J) and therefore there are no economic studies included in this review.

1.1.7.2 Excluded studies

All the excluded studies with reasons for exclusion can be found in Appendix J.

1.1.8 Summary of included economic evidence

There are no existing economic studies for this review question.

1.1.8.1 Economic model

No economic modelling was completed for this review question.

1.1.8.2 Unit costs

Resource	Unit costs	Source
Dapagliflozin 10mg (per day)	£1.30	BNF
Dulaglutide 0.75mg (per day)	£2.62	BNF
Dulaglutide 1.5mg (per day)	£2.62	BNF
Empagliflozin 10mg (per day)	£1.31	BNF
Empagliflozin 25mg (per day)	£1.31	BNF
Exenatide 2mg (per day)	£2.62	BNF
Insulin detemir 100 U/mL (per day)	£2.80	BNFc
Insulin detemir 200 U/mL (per day)	£5.60	BNFc
Linagliptin 5mg (per day)	£1.19	BNF
Liraglutide 1.8mg (per day)	£3.92	BNFc
Metformin 500mg (per day, tablet)	£0.03	BNFc
Metformin 500mg (per day, modified-release tablet)	£0.03	BNFc

Resource	Unit costs	Source
Metformin 500mg/5ml (per day, Oral solution)	£1.29	BNFc
Metformin 500mg (per day, Powder)	£0.33	BNFc
NPH (isophane) insulin 100 U/mL (per day)	£1.57	BNFc
NPH (isophane) insulin 200 U/mL (per day)	£3.14	BNFc
Sitagliptin 100mg (per day)	£1.19	BNF

1.1.9 The committee's discussion and interpretation of the evidence

1.1.9.1. The outcomes that matter most

The committee identified glycated haemoglobin level (HbA1c), glucose level, change from baseline in BMI z-score, number of participants needing rescue medication in form of insulin, and remission of type 2 diabetes as critical outcomes. Important outcomes were identified as serious adverse events (in particular, diabetic ketoacidosis/hyperosmolar hyperglycaemic state; severe hypoglycaemic episode; pancreatitis), gastrointestinal symptoms (abdominal discomfort, diarrhoea, nausea, vomiting), effects on co-morbidities, quality of life and mental health outcomes (including diabetes distress). Change in BMI z-score was chosen as a critical outcome as obesity is a known risk factor for type 2 diabetes in children and young people. The committee noted that it was likely that studies would report fasting plasma glucose level but indicated that more recent measures of glucose level (such as time in range) would be preferable. Effects on co-morbidities was chosen as an important outcome because children and young people with type 2 diabetes often have co-morbidities which may affect or be affected by treatment.

The committee acknowledged that avoiding gastrointestinal side effects is an important consideration for children and young people with type 2 diabetes but as treatment options are limited, treatment decisions may be difficult to base primarily on self-reported adverse events. Care should be taken with medication titration to limit experienced side effects and therefore support adherence.

No evidence was identified that examined the following outcomes for any comparison: remission of Type 2 Diabetes; effects on co-morbidities; quality of life; and mental health outcomes (including diabetes distress).

1.1.9.2 The quality of the evidence

Second-line treatment alternative to metformin

One RCT (Shankar 2022) was identified that compared a DPP-4 inhibitor (sitagliptin) to placebo for 20 weeks followed by metformin for 34 weeks in treatment-naïve children and young people with type 2 diabetes. The quality of evidence ranged from low to very low quality. The trial was at high risk of bias due to serious concerns about the randomisation process (no information about process, differences in baseline characteristics) and some concerns about missing data. Furthermore, all the outcomes were downgraded due to serious or very serious imprecision in the 95% confidence intervals.

Metformin combination therapy

GLP-1 receptor agonists

Overall, the evidence for using GLP-1 receptor agonists (GLP-1 RAs) with metformin compared to metformin monotherapy ranged from high to very low for the critical outcomes (HbA1c % change, mean glucose level change, BMI z-score, insulin rescue medication) and low to very low for the important outcomes (e.g. serious adverse events, other gastrointestinal symptoms).

The evidence for liraglutide from 1 RCT (Tamborlane 2019) was of moderate to low quality for the critical outcomes and very low quality for all important outcomes. The trial was well reported and at low risk of bias with some outcomes downgraded for serious or very imprecision in the 95% confidence intervals. For long-term adverse event outcomes, the quality of evidence was downgraded due to the open-label nature of this part of the trial. The committee also agreed that although the trial was relatively small (at least compared to studies on adults with type 2 diabetes), this is to be expected given the difficulty – due to the relative low prevalence of the disease - in recruiting children and young people with type 2 diabetes into clinical trials. As such, they agreed that it is unlikely that substantively better-quality trial evidence will be obtainable.

Serious heterogeneity (i^2=64%) was identified for the outcome of number of participants achieving an HbA1c %<7% in the short term (that is, less than 26 weeks). Although the 95% CI for exenatide crossed the line of no effect, the study only contributed 11% weight to the overall effect estimate and the other two (for dulaglutide and liraglutide) estimates were in the same general direction (that is, favouring GLP-1 RAs). This outcome was therefore not downgraded for inconsistency. The effect estimate for liraglutide contributed just over 50% weight to the overall effect estimate, was closer to the line of no effect, and had narrower 95% confidence intervals than either of those for dulaglutide and exenatide. Removing this trial from the meta-analysis reduced heterogeneity to 0%. The forest plot for this outcome and the subgroup analysis can be found in Appendix F – GRADE tables.

The evidence for dulaglutide from 1 RCT (Arslanian 2022) ranged from low to very low quality for all outcomes. The trial was of moderate risk of bias with some concerns about the randomisation process (no information provided about process). Outcomes for dulaglutide were further downgraded due to serious indirectness (22% of participants were not receiving metformin therapy) and serious or very serious imprecision in the 95% confidence intervals.

The evidence for exenatide from 1 RCT (Tamborlane, Bishai 2022) ranged from low to very low quality for all outcomes. The trial was of moderate risk of bias with some concerns about the randomisation process (no information provided about process). Outcomes for exenatide were further downgraded due to serious indirectness (9% of participants were not receiving metformin therapy) and serious or very serious imprecision in the 95% confidence intervals.

Evidence from specific outcomes involving the trials on dulaglutide and exenatide (for example, short-term serious adverse events) were downgraded for indirectness because some of the participants (~22% and ~9%, respectively) were not also receiving metformin therapy at the beginning of the trials.

SGLT2 inhibitors

The evidence from 2 RCTs for using SGLT2 inhibitors with metformin compared to metformin monotherapy ranged from moderate to very low quality for the critical outcomes and low to very low quality for the important outcomes.

One RCT (Tamborlane, Laffel 2022) was identified that compared dapagliflozin to placebo, in addition to metformin therapy. The quality of evidence was very low for all identified outcomes. The trial was at moderate risk of bias with some concerns about the randomisation process (with some differences on baseline characteristics of ethnicity/race, fasting plasma glucose level, BMI, and basal insulin use) and missing data. Evidence was further downgraded due to some concerns about indirectness (26% of the trial participants were young adults, aged 18-24 years) and serious or very serious imprecision in the 95% confidence intervals.

One three-arm RCT (Laffel 2023) was identified that compared empagliflozin (an SGLT2 inhibitor), linagliptin (a DPP-4 inhibitor) and placebo. The quality of evidence ranged from high to low quality for the critical outcomes and from low to very low quality for the important outcomes. Approximately 91% of the participants were on metformin with or without insulin. The trial was well reported and at low risk of bias. The trial did not report BMI z-score but did report weight in kilograms as an outcome. This was used a proxy measure for the effect of the treatment on BMI z-score and downgraded one level for indirectness. Evidence was downgraded due to serious or very serious imprecision in the 95% confidence intervals.

Other comparisons

Three RCTs contributed to evidence for the three remaining comparisons. The committee agreed that the quality of evidence for the relevant interventions – insulin regimens and DPP-4 inhibitors – was not sufficient to merit recommendations about their use with metformin.

One RCT (Wheeler 2018) was identified that examined the use of insulin regimens in addition to metformin therapy to effectively manage blood glucose levels. This trial compared a long-acting insulin regimen (insulin detemir) to an intermediate-acting insulin regimen (neutral protamine Hagedorn insulin). The trial was at high risk of bias due to serious concerns about the randomisation process (no information provided about process, differences in baseline characteristics) and concerns related to lack of blinding due to the open-label nature of trial. In addition, the trial was terminated early by the sponsor due to problems recruiting sufficient participants and was therefore substantially underpowered. All outcomes were of very low quality and most outcomes were also downgraded due to serious or very serious imprecision in the 95% confidence intervals.

One three-arm RCT (Laffel 2023) was identified that compared linagliptin, a DPP-4 inhibitor (and empagliflozin, a SGLT2 inhibitor) to placebo. Approximately 91% of the participants were also on metformin with or without insulin. The quality of the evidence ranged from high to low quality for critical outcomes and low quality for important outcomes. The trial was well reported and at low risk of bias. BMI z-score was not reported but weight in kilograms was used as a proxy for this and downgraded one level for indirectness. Outcomes were downgraded for serious or very serious imprecision in the 95% confidence intervals.

One RCT (Jalaludin 2022) was identified that compared a fixed-dose combination of a DPP-4 inhibitor (sitagliptin) and metformin to metformin monotherapy. The evidence ranged from moderate to very low quality. The trial was at high risk of bias due to some concerns regarding randomisation process (no information provided about process; differences between the proportion of 10- to under-15-year-olds in each group) and high risk of bias regarding missing data in trial. Outcomes were further downgraded due to serious or very serious imprecision in the 95% confidence intervals.

1.1.9.3 Benefits and harms

Second-line alternative to metformin

Why the committee made the recommendations.

The evidence for using sitagliptin as a second-line alternative to metformin shows that, although it appears relatively safe - with no increased risk of experiencing serious adverse events and other gastrointestinal symptoms compared to placebo and metformin - it is no more effective for improving glycaemic control in either the short term (compared to placebo at 20 weeks) or the long term (compared to

metformin for a subsequent 34 weeks). Only one outcome, long-term HbA1c percentage, showed a clinically meaningful difference between groups at 54 weeks, favouring the placebo/metformin group, with people in the sitagliptin group having a higher HbA1c % level (mean difference of 0.6% [95% CI: 0.18 to 1.02]) than people in the 20-week placebo/34-week metformin group. Given the overall lack of differences for sitagliptin on all but one of the outcomes, compared to placebo after 20 weeks and metformin after a subsequent 34 weeks, the committee agreed that the evidence was not sufficient to recommend it as a second-line alternative to metformin.

Metformin combination therapy

Education and information

Why the committee made the recommendations.

Type 2 diabetes in children and young people can be effectively managed through a combination of behaviour adjustments (e.g. diet), blood glucose monitoring, and glucose-lowering agents and made recommendations to provide relevant information and education. The committee noted that in the 2015 guideline, there were (unlike for type 1 diabetes) no recommendations about education and information for children and young people with type 2 diabetes. They agreed, using their knowledge and experience, that their new recommendations merited new recommendations about education and information for children and young people with type 2 diabetes, and their families or carers. Recommendations about providing education and information were also made about insulin therapy and continuous glucose monitoring.

How the recommendations might affect practice

The recommendations are not expected to substantially affect practice.

At diagnosis

Why the committee made the recommendations.

The committee agreed, using their knowledge and experience that children and young people with type 2 diabetes are not always cared for in a specialist paediatric diabetes clinic by a multidisciplinary team. In this case, they are not able to access additional essential services such as telephone or mental health support. They therefore made a recommendation to ensure equal access so that a specialist review occurs in this setting where diagnosis can be confirmed and care, immediate and continuing, be provided.

The committee agreed that the 2015 recommendation should be amended to explicitly offer a metformin monotherapy formulation at diagnosis and to reflect the

fact that both dietary management and capillary blood glucose monitoring to monitor one's own glucose levels are both now standard care.

Various formulations of metformin are available – for example, standard- or modified-release tablets, oral solutions and powders for oral solution - but only the standard-release tablets are licensed for use in a paediatric population. As of March 2023, use of other formulations would be off label. However, the committee left the choice of metformin monotherapy formulation open on the basis that:

- alternative formulations may be more acceptable or better tolerated and it is common practice for these to be used off label in such cases
- the unit cost per day of modified-release tablets is the same as that of standard-release tablets.

The committee also noted that an additional benefit of some capillary blood test meters is that they allow people to upload their blood glucose profile data to a PC or share it online. This data can then be shared on a regular basis with the relevant healthcare professionals to enable them to make treatment recommendations in a timely manner.

The committee agreed, based on their knowledge and experience, that a high HbA1c level at diagnosis (69 mmol/mol [8.5%]) justifies adding insulin therapy to metformin to reduce:

- blood glucose levels, and so reduce the risk of hyperglycaemia
- the risk of developing diabetic ketoacidosis
- the risk of hyperglycaemia-related complications in the long term.

They did not specify which insulin therapy should be used (for example, short-, long-, or intermediate- acting) because they agreed that this choice should be left to the relevant healthcare professional, to afford clinicians flexibility given the heterogeneity of the paediatric type 2 diabetes population.

The committee also agreed that the presence of ketosis indicates a current insulin deficiency. The presence of ketosis – a metabolic state in which the body uses fat and ketones for energy rather than glucose – in children and young people with symptoms of type 2 diabetes at diagnosis suggests that they are currently insulin deficient and therefore an increased risk of developing diabetic ketoacidosis (see recommendations 1.4.1 to 1.4.63). The committee indicated that the presence of ketosis in a child or young person with apparent type 2 diabetes makes it unclear at this stage in the pathway whether the child or young person actually has type 1 or type 2 diabetes. The committee therefore recommended, based on their knowledge and experience, that this subgroup of children and young people should be offered a multiple daily basal-bolus insulin injection to both allow a differential diagnosis

between the two types of diabetes (that is, if the insulin deficiency resolves then type 2 diabetes can be confirmed) and ensure as a matter of safety that diabetic ketoacidosis does not develop. As such, the committee noted that in this context that a substantial proportion of this subgroup may have their initial diagnosis adjusted as it becomes clear whether the insulin deficiency is temporary and not symptomatic of type 1 diabetes.

How the recommendations might affect practice

The recommendations are not expected to substantially affect practice because dietary management is standard practice in the UK. It is also standard practice for different metformin formulations to be used because some children and young people prefer formulations other than the standard-release tablet. Given the relatively small number of children and young people with type 2 diabetes in the UK (1560 as of 2020), neither the provision of equipment for capillary blood glucose monitoring nor the provision of insulin is expected to exceed a significant resource impact.

Monitoring blood glucose levels and reviewing treatment

Why the committee made the recommendations.

The committee agreed using their knowledge and experience that, for children and young people with type 2 diabetes, it is important to:

- achieve an HbA1c level of 48 mmol/mol (6.5%) or lower as early as possible in the treatment pathway to avoid later complications (such as cardiovascular, kidney and liver disease) and
- avoid staying on the same treatment for too long without reassessing its effectiveness or escalation if not effective.

The committee agreed that current guidance to measure HbA1c levels every 3 months should be retained but supplemented by new recommendations to make provision for more frequent review with the use of glucose data from capillary or continuous glucose monitoring. This will allow trends in glucose data to be detected quicker than reliance on HbA1c levels alone. The committee agreed that to avoid diabetes-related complications developing (e.g. cardiovascular disease, kidney and liver disease), that an HbA1c level of 48 mmol/mol (6.5%) or lower should be targeted by children and young people with type 2 diabetes. This target was chosen because this can be used to diagnose the presence of type 2 diabetes and staying below this level is recommended to minimise the risk of long-term complications in the NICE guideline for diabetes (type 1 and type 2) in children and young people (recommendation 1.3.31).

The committee agreed, using their knowledge and experience, that a first visit after diagnosis to review glucose data should occur after 4 weeks of metformin monotherapy and subsequently, at least every 3 months. A period of 4 weeks was agreed by the committee for 3 reasons. First, at least 4 weeks blood glucose data is needed to assess treatment progress, for example whether diabetes has improved or whether treatment should be escalated. Second, although current guidance is for the first clinical visit 3-months after diagnosis, in practice this occurs earlier because newly diagnosed children and young people with type 2 diabetes often need more support than those whose glucose levels have already stabilised. For example, they may find it difficult to adhere to treatment or may need help using capillary blood glucose monitoring or continuous glucose monitoring. Third, for children and young people with type 2 diabetes who – due to a high HbA1c level of more than 69 mmol/mol [8.5%] or the presence of ketosis - are also on insulin therapy, safely reducing and stopping insulin typically takes between 2 to 6 weeks. So a review at 4 weeks to assess CGM data is of additional clinical benefit for this group.

Given the above considerations and the heterogeneity of children and young people with type 2 diabetes, the committee agreed that healthcare professionals should review subsequent treatment progress at least every 3 months (the recommended frequency of HbA1c measurements) but recognised (and allowed for the fact) that this may be required earlier (especially if the child or young person is on insulin therapy).

The committee also acknowledged that there are rare cases in which HbA1c measurements may not be valid (for example, when the child or young person has abnormal haemoglobin levels) and, using their knowledge and experience, recommended three alternative methods of estimating average glycaemia for use in such cases.

Furthermore, they agreed that the frequency of monitoring should be appropriate to the treatment and whether they are also using continuous glucose monitoring (CGM, see below) because some children and young people will require more frequent monitoring than others (e.g. those on insulin). For example, children and young people with type 2 diabetes who are on insulin but who are not using CGM will need to test their capillary blood glucose 4 to 5 times a day, whilst those using insulin and CGM will not need to use capillary blood glucose monitoring. As blood glucose levels stabilise on treatment (e.g. metformin), frequency of capillary blood glucose monitoring can be reduced. As such, enough test strips should be prescribed to enable them to self-monitor as required by their treatment until the next review.

How the recommendations might affect practice

The recommendations on capillary blood glucose monitoring and an initial review 4 weeks after diagnosis reflect current practice in England and so are not expected to have a significant impact.

Continuous glucose monitoring

Why the committee made the recommendations.

CGM is already recommended for everyone with type 1 diabetes and in some adults with type 2 diabetes, and the committee agreed that children and young people with type 2 diabetes should be offered the same. The committee's decision to include these recommendations was also based on the following:

- Type 2 diabetes in children and young people is the most aggressive form of the disease, and this population will live with the condition for longer than adults with type 2 diabetes, so timely intervention is important to reduce the risk of developing severe long-term (and possibly life-threatening) complications, such as peripheral neuropathy.
- Many children and young people experience health inequalities because of comorbidities (for example, special educational needs or learning disabilities), which can make it difficult for them to conduct capillary blood glucose measurements.
- Capillary blood glucose monitoring often requires several finger prick tests a day, which can be painful, tiring, stressful and have a negative psychological impact on the person. CGM provides another, less invasive, way for children and young people with diabetes to manage their blood glucose levels.
- CGM allows the child or young person (and their families or carers) to monitor their own glucose levels on demand and modify their behaviour or treatment accordingly.
- Some CGM devices also allow glucose data to be shared electronically.
- Using CGM, even in the short term, is likely to improve the child or young person's understanding of their own blood glucose patterns because of the continuous and visual way CGM allows glucose data to be presented (e.g. glucose rate of change [ROC] arrows).

The evidence base for the effectiveness of CGM in this population is limited, mostly because of the small number of children and young people with type 2 diabetes (1560 aged 18 and under in all NHS settings as of 2020). As a result, the committee based recommendations on CGM for this population on the recommendations about CGM for children and young people with type 1 diabetes, in this guideline, and for adults, in NICE's guideline on type 2 diabetes in adults.

The 2022 evidence review on the effectiveness of CGM to improve blood glucose level management in children and young people with type 1 diabetes concluded that:

- real-time CGM (rtCGM) is more effective than capillary blood glucose monitoring
- intermittently scanned CGM (isCGM) is no more effective than capillary blood glucose monitoring.

Therefore, the committee agreed that rtCGM should be considered when children and young people with type 2 diabetes are on insulin therapy because of:

- the increased risk of hypoglycaemia,
- comorbidities associated with type 2 diabetes in children and young people and
- the decreasing costs over time of available and appropriate devices.

As for adults, the committee agreed that CGM should not be considered for all children and young people with type 2 diabetes because some will be able to maintain their blood glucose levels within the target range using glucose-lowering agents that do not increase the risk of hypoglycaemia (such as metformin monotherapy). The option to consider isCGM for people over 4 years old was provided because some children and young people with type 2 diabetes have difficulties using rtCGM or may prefer isCGM to rtCGM.

The committee agreed that a stronger recommendation to offer rtCGM to three specific groups was justified, regardless of whether they are receiving insulin therapy, because of the child or young person's individual needs and the treatment burden associated with capillary blood glucose monitoring.

Regardless of the reason the child or young person with type 2 diabetes is offered CGM, the committee agreed that it should be provided by a team with expertise in its use, so that support can be provided and any issues with it can be quickly resolved.

The committee agreed that continuous glucose monitoring should not replace capillary blood glucose monitoring because it is still needed both for checking the CGM device and as a backup and made some further recommendations about choosing and using a CGM device, to encourage adherence and provide support.

Finally, the committee agreed, in line with the recommendations for children and young people with type 1 diabetes, that inequalities in access and uptake of CGM may still occur for those with type 2 diabetes, so they added a recommendation to address this. For example, obesity and type 2 diabetes are also closely associated, as are childhood obesity and socioeconomic status (it is highest among children living in the most deprived areas).

How the recommendations might affect practice

CGM is already recommended, with some restrictions, for adults with type 2 diabetes who are on multiple daily insulin injections or for those who otherwise need help to

monitor their blood glucose. The committee agreed that it is likely that children and young people will need to use CGM at some point in their lives so the recommendation in this review will simply introduce it into children and young people's lives earlier than it otherwise would be. The availability of devices for real-time or intermittently scanned continuous glucose monitoring (CGM) that allow remote sharing of data is increasing, although there can be wide variation in their cost. Some children or young people will also not have access to a mobile phone or compatible electronic device, which the CGM devices may require, and so some provision for this may be needed. However, the number of children and young people with type 2 diabetes who will be eligible for CGM will also be relatively low. So the recommendations to consider or offer CGM is unlikely to have a significant resource impact.

When to reduce insulin and risk of hypoglycaemia

Why the committee made the recommendations.

The committee recognised that insulin use substantively increases the risk of developing hypoglycaemia and weight gain and that it should be gradually reduced and stopped when glycaemic control is achieved. The committee chose three criteria, based on those recommended for type 1 diabetes (see recommendation 1.2.55), for when to gradually reduce (with the aim of stopping) insulin therapy in children and young people with type 2 diabetes who have been on it from diagnosis because they have high HbA1c levels or ketosis is present.

The committee recognised that the choice of how frequently glucose levels could exceed the target ranges was somewhat arbitrary although they were keen to avoid pathologizing single high glucose events and agreed that having low glucose levels more often than not (e.g. four or more days a week) would certainly indicate that insulin needs reducing.

How the recommendations might affect practice

The recommendations are not expected to substantially affect practice.

Adding liraglutide, dulaglutide, or empagliflozin to metformin

The committee made separate recommendations about combining metformin with other glucose-lowering agents for children and young people with type 2 diabetes who are or who are not on insulin therapy because insulin therapy is associated with specific risks (e.g. hypoglycaemia) not associated with metformin monotherapy. However, the overall rationale for these recommendations remains broadly the same and any differences relating to insulin therapy are noted below.

Why the committee made the recommendations

Thresholds for adding liraglutide, dulaglutide, or empagliflozin to metformin

The committee chose three thresholds for when to initiate metformin therapy with liraglutide, dulaglutide, or empagliflozin at this point in the treatment pathway in children and young people with type 2 diabetes. These thresholds reflect the chosen HbA1c threshold and upper limits of the blood glucose target ranges mentioned in the previous recommendation.

Overall, the evidence showed that two GLP-1 receptor agonists, dulaglutide and liraglutide, and one SGLT2 inhibitor, empagliflozin, were generally effective in the short term compared to placebo at reducing glucose levels in children and young people with type 2 diabetes. There were significant effects for liraglutide and dulaglutide, each compared to placebo, for the following critical outcomes:

- HbA1c % change score: mean difference -1.06 (95% CI -1.66, -0.46) and -1.4% (95% CI -1.95%, -0.85%), and
- Mean FPG level change score (mmol/L): mean difference -1.88 (95% CI -2.38, -1.11) and mean difference -2.0 (95% CI -3.0, -1.0).
- Number of participants with HbA1c %<6.5%: RR 4.26 (95% CI 1.8, 10.09) for dulaglutide
- Number of participants with HbA1c %<7.0%: RR 1.73 (95% CI 1.21, 2.48) and RR 3.75 (95% CI 1.84, 7.65)
- Rescue medication in form of insulin: RR 0.43 (95% CI 0.21, 0.86) and RR 0.17 (95% CI 0.05, 0.58)

The evidence for exenatide, which came from 1 RCT at moderate risk of bias, showed that although it was effective compared to placebo at improving HbA1c % change scores (0.85% reduction [95% CI -1.51, -0.19]), it had no effect on FPG change score, the number of participants with an HbA1c % level <7% and the number of participants needing insulin rescue medications.

The evidence for the effectiveness of liraglutide came from 1 well-reported RCT at low risk of bias; all participants were children and young people on metformin. The evidence for the effectiveness of dulaglutide, which is administered as a weekly subcutaneous injection, combined with metformin was also limited to one trial, which only reported short-term results, only 78% of participants were on metformin. There were also some concerns about how the trial was reported with few details provided about the randomisation process and allocation concealment. Nevertheless, the short-term results compared to placebo indicated that it is effective for managing glucose levels. The committee agreed that because dulaglutide is in the same class

as liraglutide and, in lieu of evidence to the contrary, that there may similarly be an increased risk of long-term gastrointestinal side effects.

The evidence for SGLT2 inhibitors showed that, compared to placebo: although empagliflozin was effective compared to placebo at improving glycaemic control in children and young people with type 2 diabetes who are receiving metformin therapy, dapagliflozin was not. The evidence for empagliflozin (but not for dapagliflozin) compared to placebo showed significant effects on the following critical outcomes:

- HbA1c % change score: -0.84% (95% CI -1.49, -0.19)
- mean FPG level change scores (mmol/L): -1.95 (95% CI -3.25, -0.65)

None of the short-term evidence for either dapagliflozin or empagliflozin showed a significant effect on other critical outcomes (glycated haemoglobin level <6.5% or <7%, BMI z-score or weight).

None of the short-term evidence for any of the identified glucose-lowering agents showed a significant effect on BMI *z*-score nor increased risk of the other important outcomes such as serious adverse events and gastrointestinal symptoms.

In the long term, evidence from one trial on liraglutide showed that effectiveness for managing glucose levels was still maintained at 54 weeks compared to placebo, with significant effects on the following critical outcomes:

- HbA1c % change score: mean difference -1.3% (95% CI -1.73, -0.87),
- mean FPG level (mmol/L): mean difference -1.81 mmol/litre (95% CI, -2.54, -1.08)
- needing insulin rescue medication during the trial: RR 0.58 (95% CI, 0.37, 0.92).

Although there was no difference on BMI *z*-score in the short-term, long-term use of liraglutide was also associated with a small reduction of 0.18 (95% CI, -0.28 to -0.08) in BMI *z*-score.

Unlike in the short term, people in the liraglutide group were 2 to 3 times as likely, compared to those in the placebo group, to experience nausea (RR 2.18 [95% CI, 1.06, 4.46]) and vomiting (RR 2.92 [95% CI,1.23, 6.95) over the entire trial period.

They agreed that these agents should be tried before insulin because of the increased risk of hypoglycaemia and weight gain associated with the latter's use. The committee limited their recommendation to children and young people aged 10 years and over because these are the licencing conditions for the use of liraglutide in a paediatric population.

Given the limited number of effective treatments to effectively manage blood glucose levels in the type 2 diabetes paediatric population, and the desire to provide children and young people with a choice of treatments, the committee agreed to make a weaker 'consider' for oral empagliflozin, an SGLT2 inhibitor, which is taken as a daily tablet. The evidence for this recommendation came from one well reported three-arm RCT, which was at low risk of bias. The weaker strength of recommendation reflected the evidence showing differences on only 2 of the critical outcomes compared to placebo.

The committee noted that there was no direct evidence identified of the effectiveness with metformin comparing any of the recommended glucose-lowering agents. They agreed that, though their recommendation meant potentially combining a GLP-1 RA or SGLT2 inhibitor with metformin earlier than they would be for an adult, such early intervention is justified by the relatively small number of available treatments for the paediatric population, the risks associated with not achieving an HbA1c level of 48 mmol/mol (6.5%) or lower, and developing diabetes-related complications. The weaker strength of recommendation for empagliflozin, an SGLT2 inhibitor, reflects the evidence suggesting that although it was also effective compared to placebo at managing blood glucose level, it did not appear to reduce the risk.

The same reasons drove the recommendation for children and young people with type 2 diabetes who are already on insulin therapy but cannot safely reduce and then stop insulin.

The committee also agreed that the lowest dose of liraglutide, dulaglutide, and empagliflozin needed to maintain the target HbA1c and blood glucose ranges specified in recommendation 1.3.48 should be maintained. This is because higher doses can lead to side effects and poorer treatment adherence. The committee observed, using their experience, that SGLT2 inhibitors are not as yet widely used in the UK paediatric population and agreed that a cross-reference to relevant MHRA and BNF advice would be useful for relevant healthcare professionals.

The committee recognised that although neither dulaglutide and empagliflozin are, as of March 2023, currently licenced for use in a paediatric population, their off-label use – as a weekly subcutaneous injection (dulaglutide) or daily tablet (empagliflozin) - is justified by the small number of effective treatments, the choice of modes of administration, and their related treatment burdens (which may be exacerbated by the child or young person's comorbidities).

Note on BMI

The committee also discussed whether BMI should be a criterion for starting treatment with glucose-lowering agents – as it is for adults – but decided that this was not needed because a small proportion of children and young people with type 2

diabetes are not overweight or obese (for example, they have an age-adjusted BMI less than 25 kg/m^2) and they did not want this group to be denied treatment on these grounds.

Choosing the appropriate glucose-lowering agent

Compared to adults, there are few available licenced treatments that can be used in combination with metformin to effectively manage blood glucose levels. The committee agreed it was of utmost importance to provide children and young people with type 2 diabetes with a choice of combination treatment as appropriate for the individual because the treatment burden associated with some medications can be substantial (often requiring several tablets or injections a day) and the needs diverse given the high prevalence of comorbidities seen in the paediatric type 2 diabetes population.

Dulaglutide is administered as a weekly injection, whereas liraglutide requires daily injections and empagliflozin is a daily oral (tablet) treatment. Because some children and young people may prefer 1 treatment regime over the other, the committee agreed to recommend both subcutaneous liraglutide and dulaglutide, and if contraindicated oral empagliflozin even though:

- There is an increased risk of nausea and vomiting associated with long-term use of liraglutide.
- There was no long-term comparative data for dulaglutide or empagliflozin.
- GLP-1 receptor agonists may be contraindicated in some children and young people with type 2 diabetes.

The committee noted, using their knowledge and experience, that some children and young people with type 2 diabetes may prefer weekly to daily injections, or they may not like injections at all and so take tablets. Equally, children and young people with type 2 diabetes who have a daily regimen may find it more convenient because both metformin and insulin also require a daily administration. Moreover, there may be stigma associated with receiving frequent daily treatment (for example, at school). Healthcare professionals (e.g., community nurses) could also administer injections rather than the child or young person (or their carer[s]) thus ensuring adherence if they attend appointments.

Other treatments

As of March 2023, in addition to liraglutide, there are four other glucose-lowering agents that are licenced for use in the UK in a paediatric population: insulin detemir, NPH insulin, exenatide (a GLP-1 RA) and dapagliflozin (an SGLT2 inhibitor). The committee agreed that the evidence for the short-term effectiveness of insulin detemir over NPH insulin for managing glucose levels was not sufficient to recommend using one rather than the other with no differences on any critical or

important outcome found in one trial. This trial was severely underpowered due to its early termination by the sponsors, with only 42 participants (out of a target of 358) recruited. There was also no difference found on any reported critical or important outcome in the short long term between a DPP-4 inhibitor (linagliptin) and placebo, and a DPP-4 inhibitor (sitagliptin)/metformin fixed dose combination and metformin monotherapy.

How the recommendations might affect practice

Liraglutide and dulaglutide are relatively expensive compared to other possible treatments but recommending them is unlikely to surpass NICE's £1 million threshold for significant resource impact. Empagliflozin is approximately half the price of both liraglutide and dulaglutide. However, there was insufficient evidence to construct a full cost effectiveness model. The committee indicated that the difference in unit cost per dose is relatively small, especially when considering the low prevalence of type 2 diabetes in children and young people. Similar considerations apply to using insulin at diagnosis where the prevalence of type 2 diabetes combined with a high HbA1c level or high blood ketones is even lower.

Increased support from a paediatric diabetic nurse and consultant will be needed when the child or young person starts on a GLP-1 receptor agonist. However, once the child or young person's HbA1c levels are stabilised, this requirement will be smaller because repeat prescriptions can be made by the GP.

Insulin therapy

Why the committee made the recommendations.

The committee based their recommendations on insulin therapy on [those for children and young people with type 1 diabetes]. Overall, the committee agreed that the choice of insulin therapy should be left to the child or young person with type 2 diabetes (or their families or carers), in consultation with the specialist diabetes paediatric team. Some general recommendations were made about choosing an insulin regimen, providing appropriate equipment for injections, reviewing injection sites, and providing additional support when glucose levels are not optimal.

How the recommendations might affect practice

Insulin is a last resort in the management of type 2 diabetes in children and young people and the recommendations are not expected to substantially affect practice.

Changing treatments and updating school healthcare plans

Why the committee made the recommendations.

The committee agreed that the paediatric diabetes team should update the child or young person's school healthcare plan annually (when they move up a school year) and when any changes to treatment that changes the care in school are agreed to enable coordination of care with the child's or young person's school.

The committee also agreed that healthcare professionals should be reminded that the possibility of changing treatment should be discussed with children and young people with type 2 diabetes (and their carer[s]), in line with recommendation 1.5.4 on service provision and the NICE guideline on shared decision making (recommendations 1.2 to 1.4).

How the recommendations might affect practice

The recommendations are not expected to substantially affect practice.

Research recommendations

In making the recommendations above, the committee acknowledged there is a lack of evidence regarding the effectiveness in children and young people with type 2 diabetes of

- weekly treatment with glucose-lowering agents for improving glycaemic control compared to daily treatment; and
- treatments that are used in the adult type 2 diabetes population.

The committee recognised that there are a substantive number of treatments licenced for use in adults with type 2 diabetes and that when a child or young person transitions from paediatric to adult services (see recommendations 1.5.10 to 1.5.14)] on the transition from paediatric to adult care), they may change treatment if appropriate. In contrast to the adult case, there are very few licenced, effective, and safe medicines to effectively manage blood glucose levels for children and young people with type 2 diabetes. The committee thus made a research recommendation for further clinical trials in children and young people of drugs used for adults.

1.1.9.4 Cost effectiveness and resource use

Overall, no relevant published economic evidence was identified, and no original economic modelling was performed for this research question. Therefore, only the unit costs of the medications were presented to the committee.

The committee acknowledged that this guideline had a different recommendation for continuous glucose monitoring (CGM) than for adults with diabetes. There is no

health economic evidence on whether CGM is cost effective in young people with type 2 diabetes; however, it was found to be cost effective in the adult population. Therefore, the committee felt that it was important to bring this in line and recommend CGM for patients on insulin or those with a condition or disability which would make finger pricking difficult. The committee assumed that around 70% of patients would take up this option and therefore it would be approximately £330,000 for those on insulin and £258,000 for those with a condition or disability that makes finger pricking difficult. These cost estimates fall below NICE's threshold of £1 million per recommendation and so are not deemed to have a significant resource impact. The committee also felt that introducing CGM to this population would help reduce health inequalities.

The committee acknowledged that they were recommending a GLP-1 receptor agonist (GLP-1 RA) in children and young people earlier in the treatment pathway than they are in adults (in whom SGLT2 inhibitors are recommended in combination with metformin, see NICE guideline for type 2 diabetes in adults: management). This was partly due to which medications are available for children and young people and, also, the clinical effectiveness evidence. In adults, the health economic evidence was very uncertain. Whilst there was some evidence that combining GLP-1 RAs with metformin may, overall, have a lower incremental cost effectiveness ratio (ICER) in people with a higher BMI (defined as greater than or equal to 30kg/m2) compared to those with a lower BMI (NICE 2022), this was not the case for all of them (for example, the ICER for liraglutide was lower in adults with a low BMI). Although the committee acknowledged that a GLP-1 RA was not the most cost-effective option in adults, not all of the medications that are available in adults are licenced in children and young people. The committee agreed that people who are diagnosed with type 2 diabetes at a younger age are much more likely to have a higher BMI compared to children who do not have it. Furthermore, the clinical evidence showed that a GLP-1 RA was beneficial in children and young people, and the costs of medications in this review are not expensive.

There was limited clinical evidence showing the benefits of empagliflozin, while dapagliflozin did not appear to be clinically effective in this population. Empagliflozin is less than half the price of liraglutide and slightly cheaper than dulaglutide. The difference in unit costs is about £2.60 more for liraglutide and about £1.30 for dulaglutide and £2.60 (per dose). Therefore, empagliflozin was added as a final line treatment if a GLP-1 RA is contraindicated or is preferred. The committee felt that the resource impact would be small especially when considering the small size of the paediatric population eligible for treatment. There was insufficient evidence to construct an economic model and so the committee could not conclude whether the recommended treatments were cost effective.

The committee agreed that these recommendations would require increased support from a paediatric diabetes nurse specialist and consultant when the child or young

person starts on a GLP-1 RA. However, when the child or young person's glycaemic control is stabilised, this requirement is reduced as repeat prescriptions can be secured from the GP.

The National Paediatric Diabetes Audit (NPDA) report for 2020/21 found 973 children and young people with type 2 diabetes being cared for in a Paediatric Diabetes Unit. The same report found that 11.4% of children and young people with type 2 diabetes were managing their diabetes through diet alone, and 40.9% were achieving the recommended target of lower or equal to 48 mmol/mol. Therefore, less than 500 children and young people would be eligible for treatment with liraglutide or dulaglutide. The resource impact will depend on the uptake of liraglutide and dulaglutide in this population but is not expected to be significant (i.e. it will be less than £1m for England).

The committee made some recommendations, which were mainly based on current and good practice, about the use of insulin therapy at diagnosis and as a 'last resort' after failure of metformin combination therapy with liraglutide, dulaglutide or empagliflozin to reduce glucose levels. The committee felt that there may be variation in practice across the country and introducing these recommendations will standardise practice. Given the relatively low number of children and young people with type 2 diabetes in England in Wales, and the even smaller number who would be eligible for liraglutide, dulaglutide and empagliflozin the committee agreed that these recommendations would not have a significant resource impact.

1.1.9.5 Other factors the committee took into account

The committee noted that children and young people with type 2 diabetes are often asymptomatic at diagnosis, estimated to be 35% in the UK and Republic of Ireland from April 2015 and April 2016 (Candler 2018), may have existing medical or mental health conditions, and may be receiving support for weight management, low self-esteem, or negative body image. As such, they may not recognise the importance of taking medication to help manage glucose levels or perceive any benefit to their wellbeing from taking it. The needs of children and young people with type 2 diabetes are therefore often complex and this should be taken into consideration when interacting with them, and their carer(s), and discussing potential treatment changes.

There were no specific equality considerations that were specifically applicable to this review.

1.1.10 Recommendations supported by this evidence review

This evidence review supports recommendations 1.3.1 to 1.3.5, 1.3.23 to 1.3.29, and 1.3.38 to 1.3.61, and the research recommendations on the effectiveness of weekly treatments with glucose-lowering agents for effectively managing glucose levels, and

trials in children and young people with type 2 diabetes of glucose-lowering agents that are effective in adults with type 2 diabetes for managing glucose levels.

1.1.11References – included studies

1.1.11.1 Effectiveness evidence

Arslanian, Silva A, Hannon, Tamara, Zeitler, Philip et al. (2022) Once-Weekly Dulaglutide for the Treatment of Youths with Type 2 Diabetes. The New England journal of medicine 387(5): 433-443

Jalaludin, Muhammad Yazid, Deeb, Asma, Zeitler, Philip et al. (2022) Efficacy and safety of the addition of sitagliptin to treatment of youth with type 2 diabetes and inadequate glycemic control on metformin without or with insulin. Pediatric diabetes 23(2): 183-193

Laffel, Lori M., Thomas Danne, Georgeanna J. Klingensmith, William V. Tamborlane, Steven Willi, Philip Zeitler, Dietmar Neubacher et al. (2023) Efficacy and safety of the SGLT2 inhibitor empagliflozin versus placebo and the DPP-4 inhibitor linagliptin versus placebo in young people with type 2 diabetes (DINAMO): a multicentre, randomised, double-blind, parallel group, phase 3 trial. The Lancet Diabetes & Endocrinology 11(3): 169-181

Shankar, R Ravi, Zeitler, Philip, Deeb, Asma et al. (2022) A randomized clinical trial of the efficacy and safety of sitagliptin as initial oral therapy in youth with type 2 diabetes. Pediatric diabetes 23(2): 173-182

Tamborlane, William V, Barrientos-Perez, Margarita, Fainberg, Udi et al. (2019) Liraglutide in Children and Adolescents with Type 2 Diabetes. The New England journal of medicine 381(7): 637-646

Tamborlane, William V, Bishai, Raafat, Geller, David et al. (2022) Once-Weekly Exenatide in Youth With Type 2 Diabetes. Diabetes care 45(8): 1833-1840

Tamborlane, William V, Laffel, Lori M, Shehadeh, Naim et al. (2022) Efficacy and safety of dapagliflozin in children and young adults with type 2 diabetes: a prospective, multicentre, randomised, parallel group, phase 3 study. The lancet. Diabetes & endocrinology 10(5): 341-350

Wheeler, Mark D, Barrientos-Perez, Margarita, Lo, Fu-Sung et al. (2018) A 26-week, randomized trial of insulin detemir versus NPH insulin in children and adolescents with type 2 diabetes (iDEAt2). European journal of pediatrics 177(10): 1497-1503

1.1.11.2 References – other

Battelino, Tadej, Danne, Thomas, Bergenstal, Richard M., et al. (2019) Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. Diabetes care 42(8): 1593-1603.

Candler, T. P., Mahmoud, O., Lynn, R. M., Majbar, A. A., Barrett, T. G., & Shield, J. P. H. (2018). Continuing rise of type 2 diabetes incidence in children and young people in the UK. Diabetic Medicine 35(6): 737-744.

Hilliard, Marisa E., Lawrence, Jean M., Modi, Avani C., et al. and SEARCH for Diabetes in Youth Study Group. (2013) Identification of minimal clinically important difference scores of the PedsQL in children, adolescents, and young adults with type 1 and type 2 diabetes. Diabetes care 36(7): 1891-1897.

Little, Randie R., and Rohlfing, Curt L. (2013) The long and winding road to optimal HbA1c measurement. Clinica chimica acta 418: 63-71.

National Institute for Health and Care Excellence (NICE). (2022) British National Formulary. Available from: https://bnf.nice.org.uk/drug/

National Institute for Health and Care Excellence (NICE). (2022) British National Formulary for Children. Available from: https://bnfc.nice.org.uk/drug/

National Institute for Health and Care Excellence (NICE) (2022) Type 2 diabetes in adults: management. Health economic model report. Available from: https://www.nice.org.uk/guidance/ng28/evidence/health-economic-model-report-pdf-10959500845

National Paediatric Diabetes Audit Annual Report 2020-21: Care Processes and Outcomes. London: Royal College of Paediatrics and Child Health, 2022. Available at: https://www.rcpch.ac.uk/sites/default/files/2022-04/National%20NPDA%20report%202020-21%20Summary%20Report.pdf

Appendices

Appendix A – Review protocols

Review protocol for glucose-lowering agents to improve glycaemic control in children and young people with Type 2 Diabetes

ID	Field	Content
0.	PROSPERO registration number	CRD42022363732
1.	Review title	Glucose-lowering agents to manage blood glucose levels in children and young people with type 2 diabetes
2.	Review question	***Guideline:*** Type 2 diabetes in children and young people: diagnosis and management (NG18) ***Question***: In children and young people with type 2 diabetes, what is the clinical and cost effectiveness of glucose-lowering agents for improving glycaemic control in combination with metformin, and as an alternative when metformin is not tolerated or glucose levels are no longer optimally controlled by it?
3.	Objective	To determine the clinical and cost effectiveness of combining metformin with other glucose-lowering agents to improve glycaemic control in children and young people with type 2

		diabetes, and to identify alternatives to metformin, which can sometimes be not well tolerated, or not provide optimal control of glucose levels.
4.	Searches	The following databases will be searched: Clinical searches: o Cochrane Central Register of Controlled Trials (CENTRAL) o Cochrane Database of Systematic Reviews (CDSR) o Embase o MEDLINE ALL Economic searches: o Econlit o Embase o HTA o INAHTA o MEDLINE ALL o NHS EED Searches will be restricted by: o English language o Study designs of RCTs and SRs will be applied o Animal studies will be excluded from the search results o Conference abstracts will be excluded from the search results o Date of last search for this review question in NG18 (2015), conducted in August 2014 Other searches:

		○ N/A The full search strategies for each database will be published in the final review in line with the PRISMA-S reporting guide.
5.	Condition or domain being studied	Type 2 Diabetes
6.	Population	Children and young people with Type 2 diabetes 'Children and young people' is defined as people ≤18 years-old
7.	Intervention	The following interventions will be considered either on their own as second-line treatment when metformin not well tolerated or when diabetes is not optimally controlled by it, or in combination with metformin: • Dipeptidyl peptidase-4 (DPP-4) inhibitor (e.g. alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin) • Glucagon-like peptide-1 (GLP-1) receptor agonist (e.g. dulaglutide, exenatide [Byetta®, Bydureon®], liraglutide [Victoza®], lixisenatide, semaglutide) • Insulin regimen ○ Very-fast acting (e.g. Fiasp (aka: insulin aspart)) ○ Rapid acting (e.g. glulisine, lispro,) ○ Intermediate acting (e.g. Neutral protamine Hagedorn (NPH) insulin (aka: isophane insulin)

		○ Long acting (e.g. insulin detemir, insulin glargine, insulin degludec) • Meglitinide (e.g. repaglinide, nateglinide) • Sodium-glucose co-transporter 2 (SGLT2) inhibitors (e.g. canagliflozin, dapagliflozin, empagliflozin) • Sulfonylurea (e.g. glipizide [Glucotrol®], gliclazide [Diamicron®], glimepiride [Amaryl®], glyburide [DiaBeta®, Glynase®], tolbutamide) • Thiazolidinedione (e.g. pioglitazone)
8.	Comparator	For studies on second-line treatments as alternative to metformin when metformin is not tolerated: • Any other combination of listed intervention (including insulin) + or – placebo • Placebo/Usual care (can include lifestyle advice, diet and physical activity, diabetes education, and/or use of medication) For metformin combination therapy: • Metformin monotherapy • Metformin + any other combination of listed intervention (including insulin) + or – placebo • Metformin + placebo
9.	Types of study to be included	• Phase 3 and Phase 4 RCTs • Systematic review of RCTs
10.	Other exclusion criteria	• Studies on glucose-lowering agents that are not currently available in the UK will be excluded

		• Studies that include mixed populations (e.g. children, young people, and adults; pre-diabetes, Type 1 diabetes, and/or Type 2 diabetes) will be included only if data has been reported for the subgroup of children and young people. If the data has not been reported separately then studies will be excluded if:
		  ○ ≤70% of the participants have Type 2 diabetes OR
		  ○ ≤50% of people are aged ≤18 years-old.
		• Non-English language studies
		• Conference abstracts

11.	Context	This review is part of an update of the NICE guideline on Type 1 and Type 2 diabetes in children and young people: diagnosis and management (NG18): https://www.nice.org.uk/guidance/ng18 This update covers glucose-lowering treatments for improving glycaemic control in children and young people with type 2 diabetes. This guideline will also cover all settings where NHS healthcare is provided or commissioned.
12.	Primary outcomes (critical outcomes)	All outcomes will be grouped by duration of follow-up: short-term (≤6 months, or the one nearest to 6 months if multiple time-points are given) and long-term (>6 months, or the longest one if multiple time-points are given): 1. Glycated haemoglobin (HbA1c)

		2. Glucose level, for example: • Mean fasting plasma glucose (FPG) • Interstitial glucose values from continuous glucose monitoring (CGM) o Average blood glucose o Time spent above or below target glucose range o Time spent in target glucose range 3. Change from baseline in BMI *z*-score 4. Participants needing rescue medication in form of insulin 5. Remission of Type 2 Diabetes
13.	Secondary outcomes (important outcomes)	6. Adverse events (any untoward medical occurrence not necessarily caused by intervention) • Serious Adverse Events o Diabetic Ketoacidosis (DKA)/Hyperosmolar Hyperglycaemic State (HHS) o Severe hypoglycaemic episode o Pancreatitis • Other gastrointestinal symptoms (abdominal discomfort, diarrhoea, nausea, vomiting) 7. Effect on co-morbidities (presence or not):

		• Micro-Albuminuria • Diabetic retinopathy • Fatty liver disease • Hyperlipidaemia • Hypertension • Sleep apnoea • Underlying syndromes (e.g. Trisomy 21, Prader Willi Syndrome) 8. Quality of life (continuous), including patient satisfaction – measured by validated tools (e.g. Short Form 12 [SF-12], EQ-5D, Glucose Monitoring System Satisfaction Survey [GMSS], BG Monitoring System Rating Questionnaire [BGMSRQ], Hypoglycaemia Fear Survey- II [HFS-II], DqoL, PEDSQL) 9. Mental health outcomes measured using validated questionnaires (e.g. The Problem Areas in Diabetes [PAID] questionnaire and Diabetes Distress Scale [DSS]), in particular • Diabetes distress (including fear of hypoglycaemia, daily burden, treatment burden and diabetes burnout)
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.

<table>
<tr><td></td><td></td><td>This review will make use of the priority screening functionality within the EPPI-reviewer software.

The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). Study investigators may be contacted for missing data where time and resources allow.</td></tr>
<tr><td>15.</td><td>Risk of bias (quality) assessment</td><td>Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual.

Randomised control trials (individuals or cluster) will be assessed using the Cochrane Risk of Bias (RoB) tool 2.0. Systematic reviews of RCTs will be assessed using the Risk of Bias in Systematic Reviews (ROBIS) checklist.

The overall quality of evidence for specific outcomes will be assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework. Minimally important differences (MIDs) for the following outcomes will be used in assessing imprecision in the GRADE framework:

<table>
<tr><th>Outcome</th><th>MID (Source)</th></tr>
<tr><td>HbA1c
(% or mmol/litre)</td><td>0.5 percentage points or 5.5 mmol/mol (Little 2013)</td></tr>
<tr><td>Glucose level: Time in range (%)</td><td>5% change in time in range (Battelino 2019)</td></tr>
</table>
</td></tr>
</table>

PEDS-QL	(Hilliard 2013)
PEDS-QL generic youth	4.72 score
PEDS-QL generic parent	4.88 score
PEDS-QL diabetes youth	5.27 score
PEDSQL diabetes parent	4.54 score

For continuous outcomes expressed as a mean difference where no other MID was available, an MID of 0.5 of the median standard deviations of the comparison group arms will be used (Norman et al. 2003). For relative risks where no other MID is available, default MIDS of 0.8 and 1.25 will be used. When decisions are made in situations where MIDs are not available, the 'Evidence to Recommendations' section of this review will make explicit the committee's view of the expected clinical importance and relevance of the findings. In particular, this will include consideration of whether the effect of a treatment (which may be felt across multiple independent outcome domains) is likely to be clinically meaningful as a whole.

References:

Little RR, Rohlfing CL. The long and winding road to optimal HbA1c measurement. Clin Chim Acta. 2013 Mar 15;418:63-71. Doi: 10.1016/j.cca.2012.12.026. Epub 2013 Jan 11. PMID: 23318564; PMCID: PMC4762213.

		Battelino T, Danne T, Bergenstal RM, et al. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. Diabetes Care. 2019;42(8):1593-1603. Doi:10.2337/dci19-0028 Hilliard ME, Lawrence JM, Modi AC, et al. Identification of minimal clinically important difference scores of the PedsQL in children, adolescents, and young adults with type 1 and type 2 diabetes. Diabetes Care. 2013;36(7):1891-1897. Doi:10.2337/dc12-1708
16.	Strategy for data synthesis	For details please see section 6 of Developing NICE guidelines: the manual. Meta-analysis will be conducted where appropriate. Only data for children and young people with Type 2 Diabetes will be extracted from studies on mixed populations that report data for this and other subgroups. Data regarding the following baseline characteristics will be extracted if available: • Duration of T2DM • Glycated haemoglobin • Fasting plasma glucose • Blood pressure (as percentile for age and gender, if possible) • Metformin dose • Number of participants using insulin

		• Data about the presence of the following baseline co-morbidities will be extracted if available:
		  ○ Micro-Albuminuria
		  ○ Diabetic retinopathy
		  ○ Fatty liver disease
		  ○ Hyperlipidaemia
		  ○ Sleep apnoea
		  ○ Underlying syndromes (e.g. Trisomy 21, Prader Willi Syndrome)
		
		Network meta-analysis is not planned for this review.

17.	Analysis of sub-groups	The following groups will be considered for subgroup analysis if heterogeneity is present: • Age Range: Children under 5 years old; school age children (6 – 12 years); Adolescents (>12 years). • Stage of development: Prepubertal; post-pubertal • Ethnicity (whether people are from an ethnic minority and which minority) • People with learning difficulties or autism • People who are unable to self-test

18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	September 2022		
22.	Anticipated completion date	TBC		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☑	☑

		Piloting of the study selection process	☑	☑
		Formal screening of search results against eligibility criteria	☑	☑
		Data extraction	☑	☑
		Risk of bias (quality) assessment	☑	☑
		Data analysis	☑	☑
24.	Named contact	**5a. Named contact** Guideline Updates Team **5b Named contact e-mail** Diabetesupdate@nice.org.uk		

		5c Organisational affiliation of the review National Institute for Health and Care Excellence (NICE)
25.	Review team members	From the Guideline Updates Team: • Caroline Mulvihill (Technical Adviser) • Linyun Fou (Technical Analyst) • Syed Mohiuddin (Technical Adviser – Economics) • Stephanie Armstrong (Senior Technical Analyst – Economics)
26.	Funding sources/sponsor	• This systematic review is being completed by the Guideline Development Team B, Centre for Guidelines which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website:

29.	Other registration details	None
30.	Reference/ URL for published protocol	None
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Adolescents, children, DPP-4 inhibitor, GLP-1 receptor agonist, insulin, meglitinides, metformin, SGLT2 inhibitor, sulfonylureas, thiazolidinedione, type 2 diabetes, young people
33.	Details of existing review of same topic by same authors	None
34		• ☒ • Ongoing

	Current review status	• ☐ • Completed but not published • ☐ • Completed and published • ☐ • Completed, published and being updated • ☐ • Discontinued
35	Additional information	[Provide any other information the review team feel is relevant to the registration of the review.]
36.	Details of final publication	• www.nice.org.uk

Appendix B – Literature search strategies

Review question

In children and young people with type 2 diabetes, what is the clinical and cost effectiveness of glucose-lowering agents for improving glycaemic control in combination with metformin, and as an alternative when metformin is not tolerated or glucose levels are no longer optimally controlled?

Background and development

Search design and peer review

A NICE information specialist conducted the literature searches for the evidence review. The searches were run on 05 09 2022 to 06 09 2022 and the MEDLINE ALL search was updated on 27 02 2023.. This search report is compliant with the requirements of PRISMA-S.

The MEDLINE strategy below was quality assured (QA) by a trained NICE information specialist. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2016 PRESS Checklist.

The principal search strategy was developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess 'low-probability' matches. All decisions made for the review can be accessed via the deduplication history.

Prior work

The population terms for type 2 diabetes were adapted from the following NICE guidelines: NG18 Diabetes (type 1 and type 2) in children and young people: diagnosis and management, 2022 – (Evidence Review C) and NG28 Type 2 diabetes in adults: management, 2022 (Evidence Review C). Terminology for type 1 diabetes were removed from these previous search strategies.

The intervention terms adapted from NG28 Type 2 diabetes in adults: management, 2022 (Evidence Review B). Additional medicine intervention terms were added from the review protocol for the current guideline update: K:\1-Guideline Development Team\3. Guidelines\3. In Development\Diabetes\3. Development\1. Review Protocols\Type 2 CYP meds\Protocol RQ T2D CYP Pharmacological agents CM

Limits and restrictions

English language limits were applied in adherence to standard NICE practice and the review protocol.

Limits to exclude conferences were applied to the Embase and Cochrane CENTRAL searches in adherence to standard NICE practice and the review protocol. Limits to exclude trials registry records were applied to the Cochrane CENTRAL searches in adherence to standard NICE practice.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from: Dickersin, K., Scherer, R., & Lefebvre, C. (1994). Systematic Reviews: Identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286.

Search filters and classifiers

Clinical/public health searches

Systematic reviews

The MEDLINE SR filter was "Health-evidence.ca Systematic review search filter" from Lee et al. (2012). The standard NICE modifications were used: pubmed.tw added; systematic review.pt added from MeSH update 2019.

The Embase SR filter was "Health-evidence.ca Systematic review search filter" from Lee et al. (2012). The standard NICE modifications were used: pubmed.tw added to line medline.tw.

- Lee, E. et al. (2012) An optimal search filter for retrieving systematic reviews and meta-analyses. *BMC Medical Research Methodology,* 12(1), 51.

RCTs

The MEDLINE RCT filter was McMaster Therapy – Medline – "best balance of sensitivity and specificity" version. The standard NICE modifications were used: randomized.mp changed to randomi?ed.mp.

- Haynes RB et al. (2005) Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. *BMJ*, 330, 1179-1183.

The Embase RCT filter was McMaster Therapy – Embase "best balance of sensitivity and specificity" version.

- Wong SSL et al. (2006) Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. *Journal of the Medical Library Association*, 94(1), 41-47.

Cost effectiveness searches

The following search filters were applied to the search strategies in MEDLINE and Embase to identify cost-effectiveness studies:

- Glanville J et al. (2009) Development and Testing of Search Filters to Identify Economic Evaluations in MEDLINE and EMBASE. Alberta: Canadian Agency for Drugs and Technologies in Health (CADTH)

Several modifications have been made to these filters over the years that are standard NICE practice.

The following search filters (sensitive version) were applied to the search strategies in MEDLINE and Embase to identify cost-utility studies:

Hubbard, W, Walsh N, Hudson T, Heath A, Dietz J, and Rogers G. (2022) Development and validation of paired Medline and Embase search filters for cost-utility studies. Manuscript submitted for publication.

Key decisions

Due to the limitations of the search interfaces, and the relatively small volume of content, only the population terms from the original MEDLINE search strategy were used in the following databases: Economic Evaluations Database (EED), Epistemonikos , Health Technology Assessment (HTA), and INAHTA.

Clinical/public health searches

Main search – Databases

Database	Date searched	Database platform	Database segment or version	No. of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	6th Sept 2022	Wiley	Issue 8 of 12, August 2022	2470
Cochrane Database of Systematic Reviews (CDSR)	6th Sept 2022	Wiley	Issue 9 of 12, September 2022	0
Embase	5th Sept 2022	Ovid	Embase <1974 to 2022 September 02>	1938
Epistemonikos	6th Sept 2022	Epistemonikos	Searched 6th Sept 2022	3
MEDLINE ALL	5th Sept 2022	Ovid	Ovid MEDLINE naïve ALL <1946 to	1377

			September 02, 2022>	

Re-run search – Databases

Database	Date searched	Database Platform	Database segment or version	No. of results downloaded
MEDLINE ALL	27th Feb 2023	Ovid	Ovid MEDLINE(R) ALL <1946 to February 24, 2023>	126

Search strategy history

Database name: MEDLINE

1 exp Diabetes Mellitus, Type 2/ (161329)
2 (Type* adj4 ("2" or "II" or two*) adj4 (diabete* or diabeti* or DM)).tw. (179550)
3 ((Type2 or T2 or TII) adj4 (diabete* or diabeti* or DM)).tw. (604)
4 (dm2 or t2d* or mody).tw. (46628)
5 ((autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*) adj4 (diabete* or diabeti* or DM)).tw. (35183)
6 ((Maturit* or adult* or slow*) adj4 onset* adj4 (diabete* or diabeti* or DM)).tw. (3492)
7 ((earl* or sudden onset or child*) adj4 (diabete* or diabeti* or DM)).tw. (28266)
8 ((diabete* or diabeti* or DM) adj4 (keto* or acidi* or gastropare*)).tw. (9587)
9 ((Non-insulin* or Noninsulin*) adj4 depend* adj4 (diabete* or diabeti* or DM)).tw. (12036)
10 NIDDM.tw. (6953)
11 (insulin* adj4 independ* adj4 (diabete* or diabeti* or DM)).tw. (521)
12 or/1-11 (281113)
13 exp Infant/ or Infant Health/ or Infant Welfare/ (1228046)
14 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (1062005)
15 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (2104925)
16 Minors/ (2761)
17 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (3165504)
18 exp pediatrics/ (62621)
19 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (1174344)
20 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (2187268)
21 Puberty/ (14130)
22 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (584972)
23 Schools/ (48612)
24 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (7515)
25 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (643460)
26 ("under 16*" or "under sixteen*" or "under 18*" or "under eighteen*" or "under 25*" or "under twenty five*").ti,ab. (7587)
27 or/13-26 (6415719)
28 Hypoglycemic Agents/ (74808)
29 exp Glucagon-Like Peptide 1/ (10413)
30 ((Glucagon* adj Like adj Peptide) or recombinant glucagon*).tw. (15267)
31 (GLP* adj "1").tw. (12814)
32 GLP1*.tw. (1085)
33 Exenatide/ (2805)
34 (Exenatide* or exendin* or exenasphere* or Byetta* or Bydureon* or Saxenda*).tw. (4343)
35 (incretin mimetic* or Liraglutide* or Victoza*).tw. (3666)

36 (Dulaglutide* or Trulicity*).tw. (551)
37 (Semaglutide* or Ozempic* or Rybelsus* or wegovy*).tw. (818)
38 (Lixisenatide* or Lyxumia* or Adlyxin*).tw. (481)
39 Secretagogues/ (73)
40 (secretagog* or mitiglinide* or glufast* or starlix* or enyglid* or prandin*).tw. (9669)
41 Sodium-Glucose Transporter 2/ (1556)
42 Sodium-Glucose Transporter 2 Inhibitors/ (4797)
43 (Sodium* adj4 Glucose* adj4 Transporter* adj4 "2").tw. (2331)
44 (Sodium* adj4 Glucose* adj4 (co-transporter* or cotransporter* or co transporter*) adj4 "2").tw. (5742)
45 (SGLT* or gliflozin*).tw. (7698)
46 Canagliflozin/ (892)
47 (Canagliflozin* or Invokana* or Dapagliflozin* or andatang* or edistride* or oxra* or Forxiga* or Farxiga* or Ertugliflozin* or Steglatro* or Empagliflozin* or Jardiance* or gibtulio* or oboravo* or Glyxambi* or sulisent* or canaglu*).tw. (4480)
48 exp Sulfonylurea Compounds/tu [Therapeutic Use] (5672)
49 (Sulfonylurea* or Sulphonylurea* or sulfonurea* or sulfonyl* or sulphonurea*).tw. (18412)
50 (Gliclazide* or Bilxona* or Laaglyda* or Nazdol* or Zicron* or Diamicron* or glimicron* or glycazide* or glyclazide* or nordialex* or predian*).tw. (1489)
51 (Glimepirid* or Amaryl* or glyburide* or glucovance* or amglidia* or glibenclamide* or DiaBeta* or Glynase* or euglim* or glemax* or glimerid* or glorion* or roname* or solosa*).tw. (12312)
52 (Glipizide* or Minodiab* or Glucotrol* or aldiab* or apamid* or beapizide* or decose* or depizide* or diabes* or diasef* or dibizide* or digrin* or dipazide* or gipzide* or glibenese* or glibetin* or glibinese* or glibizide* or glican* or glidiab* or glidiazinamide* or glipicontin* or glipid* or glizide* or glucatrol* or gluco-rite* or glucorite* or glucodiab* or glucolip* or glucozide* or glupitel* or glupizide* or glutrol* or glyde* or glydiazenamide* or glydiaziamide* or glydiazinamide* or glygen* or glypizide* or glyzid* or glyzip* or melizid* or mindiab* or minidiab* or napizide* or ozidia* or pezide* or sucrazide* or sunglucon*).tw. (2341)
53 (Tolbutamid* or abemin* or aglicem* or aglycid* or arcosal* or artosin* or beglucin* or butamid* or diabecid or diaben* or diabenyl* or diabesan* or diabetamid* or diabetol* or diabeton* or metilato* or diabuton* or diasulin* or diatol* or dirastan* or dolipol* or fresan* or glicemin* or glicotron* or glyconon* or glycotron* or guabeta* or hypoglycone* or ipoglicone* or ipoglucos* or meramol* or glucosulfina* or mobenol* or antiglycemikos* or diabetal* or norboral* or neobellin* or neoinsoral* or orabet* or oresan* or orinade* or orinase* or orsinon* or osdiabet* or oterben* or pramidex* or proinsul* or rastinon* or tol-tab* or tolbugen* or tolbusal* or tolbutamate* or tolbutamin* or tolbutol* or tolbutone* or tolbutylharnstoff* or tolbutylurea* or tolglybutamide* or tolsiran* or tolubetin* or toluina* or tolumid* or toluran* or tolurast* or tolylsulfonylbutylurea* or willbutamide* or yosulan*).tw. (11390)
54 Thiazolidinediones/ (11539)
55 (Thiazolidinedione* or Glitazone*).tw. (6657)
56 Pioglitazone/ (4098)
57 (Pioglit* or cereluc* or glidipion* or paglitaz* or sepioglin* or piomed* or piozone* or pioglu* or glita or glitase* or glustin* or rosiglitazone* or avandia* or nyracta* or rezult* or rossini* or venvia* or Actos* or zactos*).tw. (11870)

58 exp Dipeptidyl-Peptidase IV Inhibitors/ or Dipeptidyl Peptidase 4/ (9220)
59 (Dipeptidyl* adj2 Peptidase* adj2 ("4" or "iv") adj Inhibitor*).tw. (3386)
60 (DPP* adj2 ("4" or "iv")).tw. (7437)
61 gliptin*.tw. (312)
62 (Saxagliptin* or Onglyza* or Komboglyze* or Qtern*).tw. (765)
63 (Vildagliptin* or vidagliptin* or equa* or jalra* or vysov* or xiliarx* or Galvus*).tw. (628591)
64 (Sitagliptin* or glactiv* or ristaben* or tesabel* or tesavel* or xelevia* or Januvia*).tw. (2657)
65 (Alogliptin* or nesina* or vipidia* or Vipdomet*).tw. (536)
66 (Linagliptin* or tradjenta* or trayenta* or Trajenta* or Jentadueto* or ondero*).tw. (921)
67 Metformin/ (16775)
68 (Metformin* or bolamyn* or diagment* or glucient* or metabet* or Glucophage* or apophage* or benofomin* or dabex* or denkaform* or deson* or dextin* or diabetase* or diabetformin* or diabetmin* or diabetosan* or diabex* or diafat* or diaformin* or diametin* or diamin* or dianben* or diformin* or dimefor* or dimethylbiguanide* or dimethyldiguanide* or eraphage or espa or euform* or fluamine* or flumamine* or fornidd* or fortamet* or glafornil* or glibudon* or glifage* or gliguanid* or glucaminol* or glucofage* or glucofago* or glucoform* or glucohexal* or glucoless* or glucomet* or glucomin* or gluconil* or glucophage* or glucostop* or glucotika* or gludepatic* or glufor* or gluformin* or glukophage* or glumeformin* or glumet* or glumetza* or glupa* or glustress* or glyciphage* or glycomet* or glycon* or glycora* or glyformin* or glymet* or haurymellin* or hipoglucin* or islotin* or jesacrin* or juformin* or lyomet* or maformin* or meglucon* or meguan* or melbin* or melformin* or mellittin* or merckformin* or mescorit* or metaformin* or metfogamma* or metfoliquid* or metforal* or metformax* or methformin* or metiguanide* or metomin* or metphormin* or miformin* or dimethylguanylgu* or dimethyldiguanide* or dimethylbiguanide* or dimethylbigu* or neoform* or riomet* or risidon* or siamformet* or siofor* or thiabet* or vimetrol* or walaphage*).tw. (74326)
69 (Competact* or actoplus* or glubrava* or metact* or piomet* or politor* or Janumet* or Eucreas* or equmet* or galvumet* or galvus* or icandra* or vysov* or zomarist* or Synjardy* or gibtulio* or jardiance* or oboravo* or Vokanamet* or invokamet* or Xigduo* or ebymect* or oxramet*).tw. (256)
70 Biguanides/ (3389)
71 Biguanide*.tw. (3238)
72 exp Glycoside Hydrolase Inhibitors/ (4602)
73 glycosid*.tw. (49297)
74 (glycosyl adj4 hydrolas*).tw. (1925)
75 ((intestinal adj4 alpha adj4 amylase adj4 inhibitor*) or (intestinal adj4 alpha-amylase adj4 inhibitor*)).tw. (15)
76 ((pancreatic adj4 alpha adj4 amylase adj4 inhibitor*) or (pancreatic adj4 alpha-amylase adj4 inhibitor*)).tw. (123)
77 ((alpha-glucosid* or alphaglucosid* or alpha-glycohydrola* or alphaglycohydrola*) adj4 inhibitor*).tw. (4369)
78 Acarbose/ (1477)
79 (Acarbos* or acarphage* or adeksa* or glumida* or glucor* or gluconase* or glucar* or glicobase* or glibose* or aglucose* or eclid * or Glucobay* or precose* or rebose* or symrose* or prandase*).tw. (6665)

80 exp Insulins/ad, tu [Administration & Dosage, Therapeutic Use] (42252)
81 exp Insulin/ad, tu [Administration & Dosage, Therapeutic Use] (39972)
82 Insulin Infusion Systems/ (6202)
83 (Insulin* adj4 (treat* or therap* or administrat* or dos* or daily or regime* or program* or human* or analogue* or biphasic* or basal* or protamine* or inject* or pen* or deliver* or device* or system* or pump* or syringe* or needle* or infusion* or tablet* or neutral* or nph)).tw. (92371)
84 (Insulin* adj4 (Intermediate* or short* or long* or ultralong* or rapid* or fast*)).tw. (30871)
85 (Actrapid* or berlinsulin* or endopancrine* or novopen* or nuralin* or umuline* or velasulin* or velosulin* or Humulin* or Hypurin*).tw. (471)
86 (afrezza* or exubera* or huminsulin* or isomarv* or solumarv* or technosphere* or novolin* or orgasulin* or umuline* or wosulin* or velosulin*).tw. (2911)
87 (Aspart* or fiasp* or kixelle * or Novolog* or Novopen* or novomix* or novorapid* or trurapi*).tw. (113722)
88 (Glulisine* or Apidra*).tw. (324)
89 (Lispro* or lyspro* or admelog* or Humalog* or liprolog* or liumjev* or lyumjev* or urli*).tw. (1281)
90 (Insulin* adj4 zinc* adj4 suspension*).tw. (95)
91 (Detemir* or Levemir*).tw. (963)
92 (Glargine* or Lantus* or Toujeo* or soliqua* or abasaglar* or abasria* or basaglar* or basalin* or basalog* or galactus* or glaricon* or glarzia* or lusduna* or optisulin* or recomulin*).tw. (3012)
93 (Degludec* or Tresiba*).tw. (732)
94 (Isophane* or Insulatard* or Insuman* or Novomix* or mixtard*).tw. (273)
95 (Fiasp* or Lyumjev* or Suliqua* or Xultophy* or NovoRapid*).tw. (97)
96 (LY2963016 or MYK-1501D or MYK1501D or Semglee*).tw. (31)
97 Biosimilar pharmaceuticals/ (3052)
98 (biosimilar* or biologics).tw. (17190)
99 Nateglinide/ (406)
100 (Meglitinide* or Repaglinide* or actulin* or enyglid* or gluconorm* or novonorm* or rapilan* or sestrine* or Nateglinide* or fastic* or glinate* or senaglinide* or trazec* or starsis*).tw. (1604)
101 or/28-100 (1118731)
102 12 and 27 and 101 (16839)
103 (MEDLINE or pubmed).tw. (288551)
104 systematic review.tw. (234635)
105 systematic review.pt. (206003)
106 meta-analysis.pt. (166784)
107 intervention$.ti. (184896)
108 or/103-107 (617130)
109 randomized controlled trial.pt. (576279)
110 randomi?ed.mp. (1020097)
111 placebo.mp. (238916)
112 or/109-111 (1083366)
113 108 or 112 (1536721)
114 102 and 113 (2619)
115 animals/ not humans/ (5008354)
116 114 not 115 (2597)

117 limit 116 to english language (2539)
118 limit 117 to yr="2014 -Current" (1377)

Database name: Embase

1 diabetes mellitus/ or non insulin dependent diabetes mellitus/ (898234)
2 (Type* adj4 ("2" or "II" or two*) adj4 (diabete* or diabeti* or DM)).tw. (277065)
3 ((Type2 or T2 or TII) adj4 (diabete* or diabeti* or DM)).tw. (2062)
4 (dm2 or t2d* or mody).tw. (81386)
5 ((autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*) adj4 (diabete* or diabeti* or DM)).tw. (43557)
6 ((Maturit* or adult* or slow*) adj4 onset* adj4 (diabete* or diabeti* or DM)).tw. (4751)
7 ((earl* or sudden onset or child*) adj4 (diabete* or diabeti* or DM)).tw. (40622)
8 ((diabete* or diabeti* or DM) adj4 (keto* or acidi* or gastropare*)).tw. (14943)
9 ((Non-insulin* or Noninsulin*) adj4 depend* adj4 (diabete* or diabeti* or DM)).tw. (14075)
10 NIDDM.tw. (8075)
11 (insulin* adj4 independ* adj4 (diabete* or diabeti* or DM)).tw. (720)
12 or/1-11 (985717)
13 exp juvenile/ or Child Behavior/ or Child Welfare/ or Child Health/ or infant welfare/ or "minor (person)"/ or elementary student/ (3854469)
14 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,ad,jw. (1367332)
15 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,ad,jw. (4186456)
16 exp pediatrics/ (119898)
17 (pediatric* or paediatric* or peadiatric*).ti,ab,in,ad,jw. (1919200)
18 exp adolescence/ or exp adolescent behavior/ or adolescent health/ or high school student/ or middle school student/ (120019)
19 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,ad,jw. (775668)
20 school/ or high school/ or kindergarten/ or middle school/ or primary school/ or nursery school/ or day care/ (119189)
21 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jw. (822665)
22 ("under 16*" or "under sixteen*" or "under 18*" or "under eighteen*" or "under 25*" or "under twenty five*").ti,ab. (11778)
23 or/13-22 (7312706)
24 antidiabetic agent/ (57644)
25 exp glucagon like peptide 1 receptor agonist/ (42311)
26 ((Glucagon* adj Like adj Peptide) or recombinant glucagon*).tw. (20820)
27 (GLP* adj "1").tw. (21509)
28 GLP1*.tw. (2041)
29 exendin 4/ (11469)
30 (Exenatide* or exendin* or exenasphere* or Byetta* or Bydureon* or Saxenda*).tw. (8402)

31 (incretin mimetic* or Liraglutide* or Victoza*).tw. (7251)
32 (Dulaglutide* or Trulicity*).tw. (1241)
33 (Semaglutide* or Ozempic* or Rybelsus* or wegovy*).tw. (1518)
34 (Lixisenatide* or Lyxumia* or Adlyxin*).tw. (941)
35 secretagogue/ (370)
36 (secretagog* or mitiglinide* or glufast* or starlix* or enyglid* or prandin*).tw. (11735)
37 sodium glucose cotransporter 2 inhibitor/ (9038)
38 sodium glucose cotransporter 2/ (4130)
39 (Sodium* adj4 Glucose* adj4 Transporter* adj4 "2").tw. (3532)
40 (Sodium* adj4 Glucose* adj4 (co-transporter* or cotransporter* or co transporter*) adj4 "2").tw. (7945)
41 (SGLT* or gliflozin*).tw. (12673)
42 canagliflozin/ (4584)
43 (Canagliflozin* or Invokana* or Dapagliflozin* or andatang* or edistride* or oxra* or Forxiga* or Farxiga* or Ertugliflozin* or Steglatro* or Empagliflozin* or Jardiance* or gibtulio* or oboravo* or Glyxambi* or sulisent* or canaglu*).tw. (8527)
44 sulfonylurea/dt [Drug Therapy] (9698)
45 exp sulfonylurea derivative/ (68029)
46 (Sulfonylurea* or Sulphonylurea* or sulfonurea* or sulfonyl* or sulphonurea*).tw. (24381)
47 (Gliclazide* or Bilxona* or Laaglyda* or Nazdol* or Zicron* or Diamicron* or glimicron* or glycazide* or glyclazide* or nordialex* or predian*).tw. (3018)
48 (Glimepirid* or Amaryl* or glyburide* or glucovance* or amglidia* or glibenclamide* or DiaBeta* or Glynase* or euglim* or glemax* or glimerid* or glorion* or roname* or solosa*).tw. (18102)
49 (Glipizide* or Minodiab* or Glucotrol* or aldiab* or apamid* or beapizide* or decose* or depizide* or diabes* or diasef* or dibizide* or digrin* or dipazide* or gipzide* or glibenese* or glibetin* or glibinese* or glibizide* or glican* or glidiab* or glidiazinamide* or glipicontin* or glipid* or glizide* or glucatrol* or gluco-rite* or glucorite* or glucodiab* or glucolip* or glucozide* or glupitel* or glupizide* or glutrol* or glyde* or glydiazenamide* or glydiaziamide* or glydiazinamide* or glygen* or glypizide* or glyzid* or glyzip* or melizid* or mindiab* or minidiab* or napizide* or ozidia* or pezide* or sucrazide* or sunglucon*).tw. (4127)
50 (Tolbutamid* or abemin* or aglicem* or aglycid* or arcosal* or artosin* or beglucin* or butamid* or diabecid or diaben* or diabenyl* or diabesan* or diabetamid* or diabetol* or diabeton* or metilato* or diabuton* or diasulin* or diatol* or dirastan* or dolipol* or fresan* or glicemin* or glicotron* or glyconon* or glycotron* or guabeta* or hypoglycone* or ipoglicone* or ipoglucos* or meramol* or glucosulfina* or mobenol* or antiglycemikos* or diabetal* or norboral* or neobellin* or neoinsoral* or orabet* or oresan* or orinade* or orinase* or orsinon* or osdiabet* or oterben* or pramidex* or proinsul* or rastinon* or tol-tab* or tolbugen* or tolbusal* or tolbutamate* or tolbutamin* or tolbutol* or tolbutone* or tolbutylharnstoff* or tolbutylurea* or tolglybutamide* or tolsiran* or tolubetin* or toluina* or tolumid* or toluran* or tolurast* or tolylsulfonylbutylurea* or willbutamide* or yosulan*).tw. (15566)
51 2,4 thiazolidinedione/ or 2,4 thiazolidinedione derivative/ (14331)
52 (Thiazolidin* or Glitazone*).tw. (13222)
53 exp glitazone derivative/ (40319)

54 (Pioglit* or cereluc* or glidipion* or paglitaz* or sepioglin* or piomed* or piozone* or pioglu* or glita or glitase* or glustin* or rosiglitazone* or avandia* or nyracta* or rezult* or rossini* or venvia* or Actos* or zactos*).tw. (17758)
55 dipeptidyl peptidase iv/ or exp dipeptidyl peptidase iv inhibitor/ (30761)
56 (Dipeptidyl* adj2 Peptidase* adj2 ("4" or "iv") adj Inhibitor*).tw. (4651)
57 (DPP* adj2 ("4" or "iv")).tw. (11346)
58 gliptin*.tw. (542)
59 (Saxagliptin* or Onglyza* or Komboglyze* or Qtern*).tw. (1649)
60 (Vildagliptin* or vidagliptin* or equa* or jalra* or vysov* or xiliarx* or Galvus*).tw. (735593)
61 (Sitagliptin* or glactiv* or ristaben* or tesabel* or tesavel* or xelevia* or Januvia*).tw. (5527)
62 (Alogliptin* or nesina* or vipidia* or Vipdomet*).tw. (931)
63 (Linagliptin* or tradjenta* or trayenta* or Trajenta* or Jentadueto* or ondero*).tw. (1864)
64 metformin/ (77809)
65 (Metformin* or bolamyn* or diagment* or glucient* or metabet* or Glucophage* or apophage* or benofomin* or dabex* or denkaform* or deson* or dextin* or diabetase* or diabetformin* or diabetmin* or diabetosan* or diabex* or diafat* or diaformin* or diametin* or diamin* or dianben* or diformin* or dimefor* or dimethylbiguanide* or dimethyldiguanide* or eraphage or espa or euform* or fluamine* or flumamine* or fornidd* or fortamet* or glafornil* or glibudon* or glifage* or gliguanid* or glucaminol* or glucofage* or glucofago* or glucoform* or glucohexal* or glucoless* or glucomet* or glucomin* or gluconil* or glucophage* or glucostop* or glucotika* or gludepatic* or glufor* or gluformin* or glukophage* or glumeformin* or glumet* or glumetza* or glupa* or glustress* or glyciphage* or glycomet* or glycon* or glycora* or glyformin* or glymet* or haurymellin* or hipoglucin* or islotin* or jesacrin* or juformin* or lyomet* or maformin* or meglucon* or meguan* or melbin* or melformin* or mellittin* or merckformin* or mescorit* or metaformin* or metfogamma* or metfoliquid* or metforal* or metformax* or methformin* or metiguanide* or metomin* or metphormin* or miformin* or dimethylguanylgu* or dimethyldiguanide* or dimethylbiguanide* or dimethylbigu* or neoform* or riomet* or risidon* or siamformet* or siofor* or thiabet* or vimetrol* or walaphage*).tw. (100478)
66 (Competact* or actoplus* or glubrava* or metact* or piomet* or politor* or Janumet* or Eucreas* or equmet* or galvumet* or icandra* or vysov* or zomarist* or Synjardy* or gibtulio* or jardiance* or oboravo* or Vokanamet* or invokamet* or Xigduo* or ebymect* or oxramet*).tw. (599)
67 exp biguanide derivative/ (114475)
68 Biguanide*.tw. (4188)
69 exp glycosidase inhibitor/ (37738)
70 glycosid*.tw. (59682)
71 (glycosyl adj4 hydrolas*).tw. (1999)
72 ((intestinal adj4 alpha adj4 amylase adj4 inhibitor*) or (intestinal adj4 alpha-amylase adj4 inhibitor*)).tw. (24)
73 ((pancreatic adj4 alpha adj4 amylase adj4 inhibitor*) or (pancreatic adj4 alpha-amylase adj4 inhibitor*)).tw. (143)
74 ((alpha-glucosid* or alphaglucosid* or alpha-glycohydrola* or alphaglycohydrola*) adj4 inhibitor*).tw. (5629)
75 exp alpha glucosidase inhibitor/ (18102)

76 (Acarbos* or acarphage* or adeksa* or glumida* or glucor* or gluconase* or glucar* or glicobase* or glibose* or aglucose* or eclid * or Glucobay* or precose* or rebose* or symrose* or prandase*).tw. (9638)
77 exp insulin derivative/ad, do, dt [Drug Administration, Drug Dose, Drug Therapy] (82888)
78 insulin infusion/ (9080)
79 (Insulin* adj4 (treat* or therap* or administrat* or dos* or daily or regime* or program* or human* or analogue* or biphasic* or basal* or protamine* or inject* or pen* or deliver* or device* or system* or pump* or syringe* or needle* or infusion* or tablet* or neutral* or nph)).tw. (133782)
80 (Insulin* adj4 (Intermediate* or short* or long* or ultralong* or rapid* or fast*)).tw. (45882)
81 (Actrapid* or berlinsulin* or endopancrine* or novopen* or nuralin* or umuline* or velasulin* or velosulin* or Humulin* or Hypurin*).tw. (5801)
82 (afrezza* or exubera* or huminsulin* or isomarv* or solumarv* or technosphere* or novolin* or orgasulin* or umuline* or wosulin* or velosulin*).tw. (5686)
83 (Aspart* or fiasp* or kixelle * or Novolog* or Novopen* or novomix* or novorapid* or trurapi*).tw. (135014)
84 (Glulisine* or Apidra*).tw. (1053)
85 (Lispro* or lyspro* or admelog* or Humalog* or liprolog* or liumjev* or lyumjev* or urli*).tw. (3661)
86 (Insulin* adj4 zinc* adj4 suspension*).tw. (57)
87 (Detemir* or Levemir*).tw. (2578)
88 (Glargine* or Lantus* or Toujeo* or soliqua* or abasaglar* or abasria* or basaglar* or basalin* or basalog* or galactus* or glaricon* or glarzia* or lusduna* or optisulin* or recomulin*).tw. (7690)
89 (Degludec* or Tresiba*).tw. (1782)
90 (Isophane* or Insulatard* or Insuman* or Novomix* or mixtard*).tw. (1584)
91 (Fiasp* or Lyumjev* or Suliqua* or Xultophy* or NovoRapid*).tw. (1163)
92 (LY2963016 or MYK-1501D or MYK1501D or Semglee*).tw. (85)
93 biosimilar agent/ (6138)
94 (biosimilar* or biologics).tw. (36280)
95 nateglinide/ (2753)
96 meglitinide/ (2148)
97 repaglinide/ (4168)
98 (Meglitinide* or Repaglinide* or actulin* or enyglid* or gluconorm* or novonorm* or rapilan* or sestrine* or Nateglinide* or fastic* or glinate* or senaglinide* or trazec* or starsis*).tw. (2653)
99 or/24-98 (1518164)
100 12 and 23 and 99 (41090)
101 (MEDLINE or pubmed).tw. (358506)
102 exp systematic review/ or systematic review.tw. (438970)
103 meta-analysis/ (255753)
104 intervention$.ti. (243632)
105 or/101-104 (863273)
106 random:.tw. (1830856)
107 placebo:.mp. (501433)
108 double-blind:.tw. (233692)
109 or/106-108 (2100956)

110 105 or 109 (2695341)
111 100 and 110 (6007)
112 nonhuman/ not human/ (5043380)
113 111 not 112 (5864)
114 limit 113 to english language (5734)
115 (conference abstract* or conference review or conference paper).db,pt. (5299770)
116 114 not 115 (3776)
117 limit 116 to yr="2014 -Current" (1938)

Database name: CDSR

#1 MeSH descriptor: [Diabetes Mellitus, Type 2] explode all trees 20214
#2 (Type* near/4 ("2" or "II" or two*) near/4 (diabete* or diabeti* or DM)):ti,ab,kw 47644
#3 ((Type2 or T2 or TII) near/4 (diabete* or diabeti* or DM)):ti,ab,kw 409
#4 (dm2 or t2d* or mody):ti,ab,kw 11753
#5 ((autoimmun* or "auto immun*" or brittle or labile or "insulin depend*" or "insulin deficien*") near/4 (diabete* or diabeti* or DM)):ti,ab,kw 406
#6 ((Maturit* or adult* or slow*) near/4 onset* near/4 (diabete* or diabeti* or DM)):ti,ab,kw 213
#7 ((earl* or "sudden onset" or child*) near/4 (diabete* or diabeti* or DM)):ti,ab,kw 4093
#8 ((diabete* or diabeti* or DM) near/4 (keto* or acidi* or gastropare*)):ti,ab,kw 1135
#9 (("Non-insulin*" or Noninsulin*) near/4 depend* near/4 (diabete* or diabeti* or DM)):ti,ab,kw 19412
#10 NIDDM:ti,ab,kw 1117
#11 (insulin* near/4 independ* near/4 (diabete* or diabeti* or DM)):ti,ab,kw 55
#12 {or #1-#11} 54876
#13 MeSH descriptor: [Infant] explode all trees 35105
#14 MeSH descriptor: [Infant Health] this term only 61
#15 MeSH descriptor: [Infant Welfare] this term only 84
#16 (prematur* or "pre-matur*" or preterm* or "pre-term*" or infan* or newborn* or "new-born*" or perinat* or "peri-nat*" or neonat* or "neo-nat*" or baby* or babies or toddler*):ti,ab,kw,so 103013
#17 MeSH descriptor: [Child] explode all trees 61855
#18 MeSH descriptor: [Child Behavior] explode all trees 2339
#19 MeSH descriptor: [Child Health] this term only 156
#20 MeSH descriptor: [Child Welfare] this term only 342
#21 MeSH descriptor: [Minors] this term only 11
#22 (child* or minor or minors or boy* or girl* or kid or kids or young*):ti,ab,kw,so 312986
#23 MeSH descriptor: [Pediatrics] explode all trees 727
#24 (pediatric* or paediatric* or peadiatric*):ti,ab,kw,so 66504
#25 MeSH descriptor: [Adolescent] this term only 110535
#26 MeSH descriptor: [Adolescent Behavior] this term only 1480
#27 MeSH descriptor: [Adolescent Health] this term only 42

#28 MeSH descriptor: [Puberty] this term only 313
#29 (adolescen* or pubescen* or prepubescen* or "pre-pubescen*" or pubert* or prepubert* or pre-pubert* or teen* or preteen* or "pre-teen*" or juvenil* or youth* or "under*age*"):ti,ab,kw,so 157538
#30 MeSH descriptor: [Schools] this term only 2532
#31 MeSH descriptor: [Child Day Care Centers] this term only 269
#32 MeSH descriptor: [Nurseries, Infant] explode all trees 12
#33 MeSH descriptor: [Schools, Nursery] this term only 40
#34 ("pre-school*" or preschool* or kindergar* or daycare or "day-care" or nurser* or school* or pupil* or student*):ti,ab,kw,so 115324
#35 ("under 16*" or "under sixteen*" or "under 18*" or "under eighteen*" or "under 25*" or "under twenty five*"):ti,ab,kw,so 16827
#36 {or #13-#35} 482260
#37 MeSH descriptor: [Hypoglycemic Agents] this term only 8520
#38 MeSH descriptor: [Glucagon-Like Peptide 1] explode all trees 1970
#39 ((Glucagon* next Like next Peptide) or recombinant glucagon*):ti,ab,kw 4172
#40 (GLP* next "1"):ti,ab,kw 3846
#41 GLP1*:ti,ab,kw 219
#42 MeSH descriptor: [Exenatide] this term only 590
#43 (Exenatide* or exendin* or exenasphere* or Byetta* or Bydureon* or Saxenda*):ti,ab,kw 1475
#44 (incretin mimetic* or Liraglutide* or Victoza*):ti,ab,kw 2187
#45 (Dulaglutide* or Trulicity*):ti,ab,kw 462
#46 (Semaglutide* or Ozempic* or Rybelsus* or wegovy*):ti,ab,kw 741
#47 (Lixisenatide* or Lyxumia* or Adlyxin*):ti,ab,kw 336
#48 MeSH descriptor: [Secretagogues] this term only 4
#49 (secretagog* or mitiglinide* or glufast* or starlix* or enyglid* or prandin*):ti,ab,kw 542
#50 MeSH descriptor: [Sodium-Glucose Transporter 2] this term only 115
#51 MeSH descriptor: [Sodium-Glucose Transporter 2 Inhibitors] this term only 536
#52 (Sodium* near/4 Glucose* near/4 Transporter* near/4 "2"):ti,ab,kw 1109
#53 (Sodium* near/4 Glucose* near/4 (co-transporter* or cotransporter* or co transporter*) near/4 "2"):ti,ab,kw 1742
#54 (SGLT* or gliflozin*):ti,ab,kw 1917
#55 MeSH descriptor: [Canagliflozin] this term only 264
#56 (Canagliflozin* or Invokana* or Dapagliflozin* or andatang* or edistride* or oxra* or Forxiga* or Farxiga* or Ertugliflozin* or Steglatro* or Empagliflozin* or Jardiance* or gibtulio* or oboravo* or Glyxambi* or sulisent* or canaglu*):ti,ab,kw 3632
#57 MeSH descriptor: [Sulfonylurea Compounds] explode all trees and with qualifier(s): [therapeutic use - TU] 1041
#58 (Sulfonylurea* or Sulphonylurea* or sulfonurea* or sulfonyl* or sulphonurea*):ti,ab,kw 3223
#59 (Gliclazide* or Bilxona* or Laaglyda* or Nazdol* or Zicron* or Diamicron* or glimicron* or glycazide* or glyclazide* or nordialex* or predian*):ti,ab,kw 631

#60 (Glimepirid* or Amaryl* or glyburide* or glucovance* or amglidia* or glibenclamide* or DiaBeta* or Glynase* or euglim* or glemax* or glimerid* or glorion* or roname* or solosa*):ti,ab,kw 2506
#61 (Glipizide* or Minodiab* or Glucotrol* or aldiab* or apamid* or beapizide* or decose* or depizide* or diabes* or diasef* or dibizide* or digrin* or dipazide* or gipzide* or glibenese* or glibetin* or glibinese* or glibizide* or glican* or glidiab* or glidiazinamide* or glipicontin* or glipid* or glizide* or glucatrol* or gluco-rite* or glucorite* or glucodiab* or glucolip* or glucozide* or glupitel* or glupizide* or glutrol* or glyde* or glydiazenamide* or glydiaziamide* or glydiazinamide* or glygen* or glypizide* or glyzid* or glyzip* or melizid* or mindiab* or minidiab* or napizide* or ozidia* or pezide* or sucrazide* or sunglucon*):ti,ab,kw 504
#62 (Tolbutamid* or abemin* or aglicem* or aglycid* or arcosal* or artosin* or beglucin* or butamid* or diabecid or diaben* or diabenyl* or diabesan* or diabetamid* or diabetol* or diabeton* or metilato* or diabuton* or diasulin* or diatol* or dirastan* or dolipol* or fresan* or glicemin* or glicotron* or glyconon* or glycotron* or guabeta* or hypoglycone* or ipoglicone* or ipoglucos* or meramol* or glucosulfina* or mobenol* or antiglycemikos* or diabetal* or norboral* or neobellin* or neoinsoral* or orabet* or oresan* or orinade* or orinase* or orsinon* or osdiabet* or oterben* or pramidex* or proinsul* or rastinon* or tol-tab* or tolbugen* or tolbusal* or tolbutamate* or tolbutamin* or tolbutol* or tolbutone* or tolbutylharnstoff* or tolbutylurea* or tolglybutamide* or tolsiran* or tolubetin* or toluina* or tolumid* or toluran* or tolurast* or tolylsulfonylbutylurea* or willbutamide* or yosulan*):ti,ab,kw 1532
#63 MeSH descriptor: [Thiazolidinediones] this term only 1271
#64 (Thiazolidinedione* or Glitazone*):ti,ab,kw 2071
#65 MeSH descriptor: [Pioglitazone] this term only 1104
#66 (Pioglit* or cereluc* or glidipion* or paglitaz* or sepioglin* or piomed* or piozone* or pioglu* or glita or glitase* or glustin* or rosiglitazone* or avandia* or nyracta* or rezult* or rossini* or venvia* or Actos* or zactos*):ti,ab,kw 5701
#67 MeSH descriptor: [Dipeptidyl-Peptidase IV Inhibitors] explode all trees 658
#68 MeSH descriptor: [Dipeptidyl Peptidase 4] this term only 112
#69 (Dipeptidyl* near/2 Peptidase* near/2 ("4" or "iv") next Inhibitor*):ti,ab,kw 1706
#70 (DPP* near/2 ("4" or "iv")):ti,ab,kw 1608
#71 gliptin*:ti,ab,kw 45
#72 (Saxagliptin* or Onglyza* or Komboglyze* or Qtern*):ti,ab,kw 495
#73 (Vildagliptin* or vidagliptin* or equa* or jalra* or vysov* or xiliarx* or Galvus*):ti,ab,kw 91172
#74 (Sitagliptin* or glactiv* or ristaben* or tesabel* or tesavel* or xelevia* or Januvia*):ti,ab,kw 2110
#75 (Alogliptin* or nesina* or vipidia* or Vipdomet*):ti,ab,kw 295
#76 (Linagliptin* or tradjenta* or trayenta* or Trajenta* or Jentadueto* or ondero*):ti,ab,kw 685
#77 MeSH descriptor: [Metformin] this term only 4525
#78 (Metformin* or bolamyn* or diagment* or glucient* or metabet* or Glucophage* or apophage* or benofomin* or dabex* or denkaform* or deson* or dextin* or diabetase* or diabetformin* or diabetmin* or diabetosan* or diabex* or diafat* or diaformin* or diametin* or diamin* or dianben* or diformin* or dimefor* or dimethylbiguanide* or dimethyldiguanide* or eraphage or espa or euform* or

fluamine* or flumamine* or fornidd* or fortamet* or glafornil* or glibudon* or glifage* or gliguanid* or glucaminol* or glucofage* or glucofago* or glucoform* or glucohexal* or glucoless* or glucomet* or glucomin* or gluconil* or glucophage* or glucostop* or glucotika* or gludepatic* or glufor* or gluformin* or glukophage* or glumeformin* or glumet* or glumetza* or glupa* or glustress* or glyciphage* or glycomet* or glycon* or glycora* or glyformin* or glymet* or haurymellin* or hipoglucin* or islotin* or jesacrin* or juformin* or lyomet* or maformin* or meglucon* or meguan* or melbin* or melformin* or mellittin* or merckformin* or mescorit* or metaformin* or metfogamma* or metfoliquid* or metforal* or metformax* or methformin* or metiguanide* or metomin* or metphormin* or miformin* or dimethylguanylgu* or dimethyldiguanide* or dimethylbiguanide* or dimethylbigu* or neoform* or riomet* or risidon* or siamformet* or siofor* or thiabet* or vimetrol* or walaphage*):ti,ab,kw 13826
#79 (Competact* or actoplus* or glubrava* or metact* or piomet* or politor* or Janumet* or Eucreas* or equmet* or galvumet* or galvus* or icandra* or vysov* or zomarist* or Synjardy* or gibtulio* or jardiance* or oboravo* or Vokanamet* or invokamet* or Xigduo* or ebymect* or oxramet*):ti,ab,kw 215
#80 MeSH descriptor: [Biguanides] this term only 198
#81 Biguanide*:ti,ab,kw 621
#82 MeSH descriptor: [Glycoside Hydrolase Inhibitors] explode all trees 180
#83 glycosid*:ti,ab,kw 1027
#84 (glycosyl near/4 hydrolas*):ti,ab,kw 6
#85 ((intestinal near/4 alpha near/4 amylase near/4 inhibitor*) or (intestinal near/4 alpha-amylase near/4 inhibitor*)):ti,ab,kw 0
#86 ((pancreatic near/4 alpha near/4 amylase near/4 inhibitor*) or (pancreatic near/4 alpha-amylase near/4 inhibitor*)):ti,ab,kw 3
#87 ((alpha-glucosid* or alphaglucosid* or alpha-glycohydrola* or alphaglycohydrola*) near/4 inhibitor*):ti,ab,kw 441
#88 MeSH descriptor: [Acarbose] this term only 352
#89 (Acarbos* or acarphage* or adeksa* or glumida* or glucor* or gluconase* or glucar* or glicobase* or glibose* or aglucose* or eclid * or Glucobay* or precose* or rebose* or symrose* or prandase*):ti,ab,kw 0
#90 MeSH descriptor: [Insulins] explode all trees and with qualifier(s): [administration & dosage - AD, therapeutic use - TU] 4740
#91 MeSH descriptor: [Insulin] this term only and with qualifier(s): [administration & dosage - AD, therapeutic use - TU] 4109
#92 MeSH descriptor: [Insulin Infusion Systems] this term only 735
#93 (Insulin* near/4 (treat* or therap* or administrat* or dos* or daily or regime* or program* or human* or analogue* or biphasic* or basal* or protamine* or inject* or pen* or deliver* or device* or system* or pump* or syringe* or needle* or infusion* or tablet* or neutral* or nph)):ti,ab,kw 30950
#94 (Insulin* near/4 (Intermediate* or short* or long* or ultralong* or rapid* or fast*)):ti,ab,kw 9384
#95 (Actrapid* or berlinsulin* or endopancrine* or novopen* or nuralin* or umuline* or velasulin* or velosulin* or Humulin* or Hypurin*):ti,ab,kw 288
#96 (afrezza* or exubera* or huminsulin* or isomarv* or solumarv* or technosphere* or novolin* or orgasulin* or umuline* or wosulin* or velosulin*):ti,ab,kw 302
#97 (Aspart* or fiasp* or kixelle * or Novolog* or Novopen* or novomix* or novorapid* or trurapi*):ti,ab,kw 0

#98 (Glulisine* or Apidra*):ti,ab,kw 328
#99 (Lispro* or lyspro* or admelog* or Humalog* or liprolog* or liumjev* or lyumjev* or urli*):ti,ab,kw 1219
#100 (Insulin* near/4 zinc* near/4 suspension*):ti,ab,kw 42
#101 (Detemir* or Levemir*):ti,ab,kw 758
#102 (Glargine* or Lantus* or Toujeo* or soliqua* or abasaglar* or abasria* or basaglar* or basalin* or basalog* or galactus* or glaricon* or glarzia* or lusduna* or optisulin* or recomulin*):ti,ab,kw 3069
#103 (Degludec* or Tresiba*):ti,ab,kw 1094
#104 (Isophane* or Insulatard* or Insuman* or Novomix* or mixtard*):ti,ab,kw 887
#105 (Fiasp* or Lyumjev* or Suliqua* or Xultophy* or NovoRapid*):ti,ab,kw 255
#106 (LY2963016 or MYK-1501D or MYK1501D or Semglee*):ti,ab,kw 56
#107 MeSH descriptor: [Biosimilar Pharmaceuticals] this term only 299
#108 (biosimilar* or biologics):ti,ab,kw 2887
#109 MeSH descriptor: [Nateglinide] this term only 108
#110 (Meglitinide* or Repaglinide* or actulin* or enyglid* or gluconorm* or novonorm* or rapilan* or sestrine* or Nateglinide* or fastic* or glinate* or senaglinide* or trazec* or starsis*):ti,ab,kw 602
#111 {or #37-#110} 1937424
#112 #12 and #36 and #111 8580
#113 "conference":pt or (clinicaltrials or trialsearch):so 632594
#114 #112 not #113 with Publication Year from 2014 to 2022, with Cochrane Library publication date Between Jan 2014 and Sep 2022, in Trials 2470 (0 CDSR)

Database name: CENTRAL

#1 MeSH descriptor: [Diabetes Mellitus, Type 2] explode all trees 20214
#2 (Type* near/4 ("2" or "II" or two*) near/4 (diabete* or diabeti* or DM)):ti,ab,kw 47644
#3 ((Type2 or T2 or TII) near/4 (diabete* or diabeti* or DM)):ti,ab,kw 409
#4 (dm2 or t2d* or mody):ti,ab,kw 11753
#5 ((autoimmun* or "auto immun*" or brittle or labile or "insulin depend*" or "insulin deficien*") near/4 (diabete* or diabeti* or DM)):ti,ab,kw 406
#6 ((Maturit* or adult* or slow*) near/4 onset* near/4 (diabete* or diabeti* or DM)):ti,ab,kw 213
#7 ((earl* or "sudden onset" or child*) near/4 (diabete* or diabeti* or DM)):ti,ab,kw 4093
#8 ((diabete* or diabeti* or DM) near/4 (keto* or acidi* or gastropare*)):ti,ab,kw 1135
#9 (("Non-insulin*" or Noninsulin*) near/4 depend* near/4 (diabete* or diabeti* or DM)):ti,ab,kw 19412
#10 NIDDM:ti,ab,kw 1117
#11 (insulin* near/4 independ* near/4 (diabete* or diabeti* or DM)):ti,ab,kw 55
#12 {or #1-#11} 54876

#13 MeSH descriptor: [Infant] explode all trees 35105
#14 MeSH descriptor: [Infant Health] this term only 61
#15 MeSH descriptor: [Infant Welfare] this term only 84
#16 (prematur* or "pre-matur*" or preterm* or "pre-term*" or infan* or newborn* or "new-born*" or perinat* or "peri-nat*" or neonat* or "neo-nat*" or baby* or babies or toddler*):ti,ab,kw,so 103013
#17 MeSH descriptor: [Child] explode all trees 61855
#18 MeSH descriptor: [Child Behavior] explode all trees 2339
#19 MeSH descriptor: [Child Health] this term only 156
#20 MeSH descriptor: [Child Welfare] this term only 342
#21 MeSH descriptor: [Minors] this term only 11
#22 (child* or minor or minors or boy* or girl* or kid or kids or young*):ti,ab,kw,so 312986
#23 MeSH descriptor: [Pediatrics] explode all trees 727
#24 (pediatric* or paediatric* or peadiatric*):ti,ab,kw,so 66504
#25 MeSH descriptor: [Adolescent] this term only 110535
#26 MeSH descriptor: [Adolescent Behavior] this term only 1480
#27 MeSH descriptor: [Adolescent Health] this term only 42
#28 MeSH descriptor: [Puberty] this term only 313
#29 (adolescen* or pubescen* or prepubescen* or "pre-pubescen*" or pubert* or prepubert* or pre-pubert* or teen* or preteen* or "pre-teen*" or juvenil* or youth* or "under*age*"):ti,ab,kw,so 157538
#30 MeSH descriptor: [Schools] this term only 2532
#31 MeSH descriptor: [Child Day Care Centers] this term only 269
#32 MeSH descriptor: [Nurseries, Infant] explode all trees 12
#33 MeSH descriptor: [Schools, Nursery] this term only 40
#34 ("pre-school*" or preschool* or kindergar* or daycare or "day-care" or nurser* or school* or pupil* or student*):ti,ab,kw,so 115324
#35 ("under 16*" or "under sixteen*" or "under 18*" or "under eighteen*" or "under 25*" or "under twenty five*"):ti,ab,kw,so 16827
#36 {or #13-#35} 482260
#37 MeSH descriptor: [Hypoglycemic Agents] this term only 8520
#38 MeSH descriptor: [Glucagon-Like Peptide 1] explode all trees 1970
#39 ((Glucagon* next Like next Peptide) or recombinant glucagon*):ti,ab,kw 4172
#40 (GLP* next "1"):ti,ab,kw 3846
#41 GLP1*:ti,ab,kw 219
#42 MeSH descriptor: [Exenatide] this term only 590
#43 (Exenatide* or exendin* or exenasphere* or Byetta* or Bydureon* or Saxenda*):ti,ab,kw 1475
#44 (incretin mimetic* or Liraglutide* or Victoza*):ti,ab,kw 2187
#45 (Dulaglutide* or Trulicity*):ti,ab,kw 462
#46 (Semaglutide* or Ozempic* or Rybelsus* or wegovy*):ti,ab,kw 741
#47 (Lixisenatide* or Lyxumia* or Adlyxin*):ti,ab,kw 336
#48 MeSH descriptor: [Secretagogues] this term only 4
#49 (secretagog* or mitiglinide* or glufast* or starlix* or enyglid* or prandin*):ti,ab,kw 542
#50 MeSH descriptor: [Sodium-Glucose Transporter 2] this term only 115

#51 MeSH descriptor: [Sodium-Glucose Transporter 2 Inhibitors] this term only 536
#52 (Sodium* near/4 Glucose* near/4 Transporter* near/4 "2"):ti,ab,kw 1109
#53 (Sodium* near/4 Glucose* near/4 (co-transporter* or cotransporter* or co transporter*) near/4 "2"):ti,ab,kw 1742
#54 (SGLT* or gliflozin*):ti,ab,kw 1917
#55 MeSH descriptor: [Canagliflozin] this term only 264
#56 (Canagliflozin* or Invokana* or Dapagliflozin* or andatang* or edistride* or oxra* or Forxiga* or Farxiga* or Ertugliflozin* or Steglatro* or Empagliflozin* or Jardiance* or gibtulio* or oboravo* or Glyxambi* or sulisent* or canaglu*):ti,ab,kw 3632
#57 MeSH descriptor: [Sulfonylurea Compounds] explode all trees and with qualifier(s): [therapeutic use - TU] 1041
#58 (Sulfonylurea* or Sulphonylurea* or sulfonurea* or sulfonyl* or sulphonurea*):ti,ab,kw 3223
#59 (Gliclazide* or Bilxona* or Laaglyda* or Nazdol* or Zicron* or Diamicron* or glimicron* or glycazide* or glyclazide* or nordialex* or predian*):ti,ab,kw 631
#60 (Glimepirid* or Amaryl* or glyburide* or glucovance* or amglidia* or glibenclamide* or DiaBeta* or Glynase* or euglim* or glemax* or glimerid* or glorion* or roname* or solosa*):ti,ab,kw 2506
#61 (Glipizide* or Minodiab* or Glucotrol* or aldiab* or apamid* or beapizide* or decose* or depizide* or diabes* or diasef* or dibizide* or digrin* or dipazide* or gipzide* or glibenese* or glibetin* or glibinese* or glibizide* or glican* or glidiab* or glidiazinamide* or glipicontin* or glipid* or glizide* or glucatrol* or gluco-rite* or glucorite* or glucodiab* or glucolip* or glucozide* or glupitel* or glupizide* or glutrol* or glyde* or glydiazenamide* or glydiaziamide* or glydiazinamide* or glygen* or glypizide* or glyzid* or glyzip* or melizid* or mindiab* or minidiab* or napizide* or ozidia* or pezide* or sucrazide* or sunglucon*):ti,ab,kw 504
#62 (Tolbutamid* or abemin* or aglicem* or aglycid* or arcosal* or artosin* or beglucin* or butamid* or diabecid or diaben* or diabenyl* or diabesan* or diabetamid* or diabetol* or diabeton* or metilato* or diabuton* or diasulin* or diatol* or dirastan* or dolipol* or fresan* or glicemin* or glicotron* or glyconon* or glycotron* or guabeta* or hypoglycone* or ipoglicone* or ipoglucos* or meramol* or glucosulfina* or mobenol* or antiglycemikos* or diabetal* or norboral* or neobellin* or neoinsoral* or orabet* or oresan* or orinade* or orinase* or orsinon* or osdiabet* or oterben* or pramidex* or proinsul* or rastinon* or tol-tab* or tolbugen* or tolbusal* or tolbutamate* or tolbutamin* or tolbutol* or tolbutone* or tolbutylharnstoff* or tolbutylurea* or tolglybutamide* or tolsiran* or tolubetin* or toluina* or tolumid* or toluran* or tolurast* or tolylsulfonylbutylurea* or willbutamide* or yosulan*):ti,ab,kw 1532
#63 MeSH descriptor: [Thiazolidinediones] this term only 1271
#64 (Thiazolidinedione* or Glitazone*):ti,ab,kw 2071
#65 MeSH descriptor: [Pioglitazone] this term only 1104
#66 (Pioglit* or cereluc* or glidipion* or paglitaz* or sepioglin* or piomed* or piozone* or pioglu* or glita or glitase* or glustin* or rosiglitazone* or avandia* or nyracta* or rezult* or rossini* or venvia* or Actos* or zactos*):ti,ab,kw 5701
#67 MeSH descriptor: [Dipeptidyl-Peptidase IV Inhibitors] explode all trees 658
#68 MeSH descriptor: [Dipeptidyl Peptidase 4] this term only 112

#69 (Dipeptidyl* near/2 Peptidase* near/2 ("4" or "iv") next Inhibitor*):ti,ab,kw 1706
#70 (DPP* near/2 ("4" or "iv")):ti,ab,kw 1608
#71 gliptin*:ti,ab,kw 45
#72 (Saxagliptin* or Onglyza* or Komboglyze* or Qtern*):ti,ab,kw 495
#73 (Vildagliptin* or vidagliptin* or equa* or jalra* or vysov* or xiliarx* or Galvus*):ti,ab,kw 91172
#74 (Sitagliptin* or glactiv* or ristaben* or tesabel* or tesavel* or xelevia* or Januvia*):ti,ab,kw 2110
#75 (Alogliptin* or nesina* or vipidia* or Vipdomet*):ti,ab,kw 295
#76 (Linagliptin* or tradjenta* or trayenta* or Trajenta* or Jentadueto* or ondero*):ti,ab,kw 685
#77 MeSH descriptor: [Metformin] this term only 4525
#78 (Metformin* or bolamyn* or diagment* or glucient* or metabet* or Glucophage* or apophage* or benofomin* or dabex* or denkaform* or deson* or dextin* or diabetase* or diabetformin* or diabetmin* or diabetosan* or diabex* or diafat* or diaformin* or diametin* or diamin* or dianben* or diformin* or dimefor* or dimethylbiguanide* or dimethyldiguanide* or eraphage or espa or euform* or fluamine* or flumamine* or fornidd* or fortamet* or glafornil* or glibudon* or glifage* or gliguanid* or glucaminol* or glucofage* or glucofago* or glucoform* or glucohexal* or glucoless* or glucomet* or glucomin* or gluconil* or glucophage* or glucostop* or glucotika* or gludepatic* or glufor* or gluformin* or glukophage* or glumeformin* or glumet* or glumetza* or glupa* or glustress* or glyciphage* or glycomet* or glycon* or glycora* or glyformin* or glymet* or haurymellin* or hipoglucin* or islotin* or jesacrin* or juformin* or lyomet* or maformin* or meglucon* or meguan* or melbin* or melformin* or mellittin* or merckformin* or mescorit* or metaformin* or metfogamma* or metfoliquid* or metforal* or metformax* or methformin* or metiguanide* or metomin* or metphormin* or miformin* or dimethylguanylgu* or dimethyldiguanide* or dimethylbiguanide* or dimethylbigu* or neoform* or riomet* or risidon* or siamformet* or siofor* or thiabet* or vimetrol* or walaphage*):ti,ab,kw 13826
#79 (Competact* or actoplus* or glubrava* or metact* or piomet* or politor* or Janumet* or Eucreas* or equmet* or galvumet* or galvus* or icandra* or vysov* or zomarist* or Synjardy* or gibtulio* or jardiance* or oboravo* or Vokanamet* or invokamet* or Xigduo* or ebymect* or oxramet*):ti,ab,kw 215
#80 MeSH descriptor: [Biguanides] this term only 198
#81 Biguanide*:ti,ab,kw 621
#82 MeSH descriptor: [Glycoside Hydrolase Inhibitors] explode all trees 180
#83 glycosid*:ti,ab,kw 1027
#84 (glycosyl near/4 hydrolas*):ti,ab,kw 6
#85 ((intestinal near/4 alpha near/4 amylase near/4 inhibitor*) or (intestinal near/4 alpha-amylase near/4 inhibitor*)):ti,ab,kw 0
#86 ((pancreatic near/4 alpha near/4 amylase near/4 inhibitor*) or (pancreatic near/4 alpha-amylase near/4 inhibitor*)):ti,ab,kw 3
#87 ((alpha-glucosid* or alphaglucosid* or alpha-glycohydrola* or alphaglycohydrola*) near/4 inhibitor*):ti,ab,kw 441
#88 MeSH descriptor: [Acarbose] this term only 352
#89 (Acarbos* or acarphage* or adeksa* or glumida* or glucor* or gluconase* or glucar* or glicobase* or glibose* or aglucose* or eclid * or Glucobay* or precose* or rebose* or symrose* or prandase*):ti,ab,kw 0

#90 MeSH descriptor: [Insulins] explode all trees and with qualifier(s): [administration & dosage - AD, therapeutic use - TU] 4740
#91 MeSH descriptor: [Insulin] this term only and with qualifier(s): [administration & dosage - AD, therapeutic use - TU] 4109
#92 MeSH descriptor: [Insulin Infusion Systems] this term only 735
#93 (Insulin* near/4 (treat* or therap* or administrat* or dos* or daily or regime* or program* or human* or analogue* or biphasic* or basal* or protamine* or inject* or pen* or deliver* or device* or system* or pump* or syringe* or needle* or infusion* or tablet* or neutral* or nph)):ti,ab,kw 30950
#94 (Insulin* near/4 (Intermediate* or short* or long* or ultralong* or rapid* or fast*)):ti,ab,kw 9384
#95 (Actrapid* or berlinsulin* or endopancrine* or novopen* or nuralin* or umuline* or velasulin* or velosulin* or Humulin* or Hypurin*):ti,ab,kw 288
#96 (afrezza* or exubera* or huminsulin* or isomarv* or solumarv* or technosphere* or novolin* or orgasulin* or umuline* or wosulin* or velosulin*):ti,ab,kw 302
#97 (Aspart* or fiasp* or kixelle * or Novolog* or Novopen* or novomix* or novorapid* or trurapi*):ti,ab,kw 0
#98 (Glulisine* or Apidra*):ti,ab,kw 328
#99 (Lispro* or lyspro* or admelog* or Humalog* or liprolog* or liumjev* or lyumjev* or urli*):ti,ab,kw 1219
#100 (Insulin* near/4 zinc* near/4 suspension*):ti,ab,kw 42
#101 (Detemir* or Levemir*):ti,ab,kw 758
#102 (Glargine* or Lantus* or Toujeo* or soliqua* or abasaglar* or abasria* or basaglar* or basalin* or basalog* or galactus* or glaricon* or glarzia* or lusduna* or optisulin* or recomulin*):ti,ab,kw 3069
#103 (Degludec* or Tresiba*):ti,ab,kw 1094
#104 (Isophane* or Insulatard* or Insuman* or Novomix* or mixtard*):ti,ab,kw 887
#105 (Fiasp* or Lyumjev* or Suliqua* or Xultophy* or NovoRapid*):ti,ab,kw 255
#106 (LY2963016 or MYK-1501D or MYK1501D or Semglee*):ti,ab,kw 56
#107 MeSH descriptor: [Biosimilar Pharmaceuticals] this term only 299
#108 (biosimilar* or biologics):ti,ab,kw 2887
#109 MeSH descriptor: [Nateglinide] this term only 108
#110 (Meglitinide* or Repaglinide* or actulin* or enyglid* or gluconorm* or novonorm* or rapilan* or sestrine* or Nateglinide* or fastic* or glinate* or senaglinide* or trazec* or starsis*):ti,ab,kw 602
#111 {or #37-#110} 1937424
#112 #12 and #36 and #111 8580
#113 "conference":pt or (clinicaltrials or trialsearch):so 632594
#114 #112 not #113 with Publication Year from 2014 to 2022, with Cochrane Library publication date Between Jan 2014 and Sep 2022, in Trials 2470

Database name: Epistemonikos

(title:((Type* AND ("2" OR "II" OR two*) AND (diabete* OR diabeti* OR DM))) OR abstract:((Type* AND ("2" OR "II" OR two*) AND (diabete* OR diabeti* OR DM)))) OR (title:(((Type2 OR T2 OR TII) AND (diabete* OR diabeti* OR DM))) OR

abstract:(((Type2 OR T2 OR TII) AND (diabete* OR diabeti* OR DM)))) OR (title:((dm2 OR t2d* OR mody)) OR abstract:((dm2 OR t2d* OR mody))) OR (title:(((autoimmun* OR auto immun* OR brittle OR labile OR insulin depend* OR insulin deficien*) AND (diabete* OR diabeti* OR DM))) OR abstract:(((autoimmun* OR auto immun* OR brittle OR labile OR insulin depend* OR insulin deficien*) AND (diabete* OR diabeti* OR DM)))) OR (title:(((Maturit* OR adult* OR slow*) AND onset* AND (diabete* OR diabeti* OR DM))) OR abstract:(((Maturit* OR adult* OR slow*) AND onset* AND (diabete* OR diabeti* OR DM)))) OR (title:(((earl* OR sudden onset OR child*) AND (diabete* OR diabeti* OR DM))) OR abstract:(((earl* OR sudden onset OR child*) AND (diabete* OR diabeti* OR DM)))) OR (title:(((diabete* OR diabeti* OR DM) AND (keto* OR acidi* OR gastropare*))) OR abstract:(((diabete* OR diabeti* OR DM) AND (keto* OR acidi* OR gastropare*)))) OR (title:(((Non-insulin* OR Noninsulin*) AND depend* AND (diabete* OR diabeti* OR DM))) OR abstract:(((Non-insulin* OR Noninsulin*) AND depend* AND (diabete* OR diabeti* OR DM)))) OR (title:(NIDDM) OR abstract:(NIDDM)) AND (title:((insulin* AND independ* AND (diabete* OR diabeti* OR DM))) OR abstract:((insulin* AND independ* AND (diabete* OR diabeti* OR DM)))) OR (title:((prematur* OR pre-matur* OR preterm* OR pre-term* OR infan* OR newborn* OR new-born* OR perinat* OR peri-nat* OR neonat* OR neo-nat* OR baby* OR babies OR toddler*)) OR abstract:((prematur* OR pre-matur* OR preterm* OR pre-term* OR infan* OR newborn* OR new-born* OR perinat* OR peri-nat* OR neonat* OR neo-nat* OR baby* OR babies OR toddler*))) OR (title:((child* OR minor OR minors OR boy* OR girl* OR kid OR kids OR young*)) OR abstract:((child* OR minor OR minors OR boy* OR girl* OR kid OR kids OR young*))) OR (title:((pediatric* OR paediatric* OR peadiatric*)) OR abstract:((pediatric* OR paediatric* OR peadiatric*))) OR (title:((adolescen* OR pubescen* OR prepubescen* OR pre-pubescen* OR pubert* OR prepubert* OR pre-pubert* OR teen* OR preteen* OR pre-teen* OR juvenil* OR youth* OR under*age*)) OR abstract:((adolescen* OR pubescen* OR prepubescen* OR pre-pubescen* OR pubert* OR prepubert* OR pre-pubert* OR teen* OR preteen* OR pre-teen* OR juvenil* OR youth* OR under*age*))) OR (title:((pre-school* OR preschool* OR kindergar* OR daycare OR day-care OR nurser* OR school* OR pupil* OR student*)) OR abstract:((pre-school* OR preschool* OR kindergar* OR daycare OR day-care OR nurser* OR school* OR pupil* OR student*))) OR (title:(("under 16*" OR "under sixteen*" OR "under 18*" OR "under eighteen*" OR "under 25*" OR "under twenty five*")) OR abstract:(("under 16*" OR "under sixteen*" OR "under 18*" OR "under eighteen*" OR "under 25*" OR "under twenty five*"))) 3 results - filtered to systematic reviews

Cost-effectiveness searches

Main search – Databases

Database	Date searched	Database Platform	Database segment or version	No. of results downloaded

EconLit	8th Sept 2022	OVID	Econlit <1886 to August 25, 2022>	14
EED	9th Sept 2022	CRD	Up to 2015	4
Embase	8th Sept 2022	Ovid	Embase <1974 to 2022 September 07>	1712
HTA	8th Sept 2022	CRD	Up to 2018	8
INAHTA	9th Sept 2022	INAHTA	Searched 9th Sept 2022	27
MEDLINE ALL	8th Sept 2022	Ovid	Ovid MEDLINE(R) ALL <1946 to September 07, 2022>	701

Re-run search – Databases

Database	Date searched	Database Platform	Database segment or version	No. of results downloaded
MEDLINE ALL	27th Feb 2023	Ovid	Ovid MEDLINE(R) ALL <1946 to February 24, 2023>	63

Search strategy history

Database name: MEDLINE ALL

1 exp Diabetes Mellitus, Type 2/ (161169)
2 (Type* adj4 ("2" or "II" or two*) adj4 (diabete* or diabeti* or DM)).tw. (179561)
3 ((Type2 or T2 or TII) adj4 (diabete* or diabeti* or DM)).tw. (605)
4 (dm2 or t2d* or mody).tw. (46644)
5 ((autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*) adj4 (diabete* or diabeti* or DM)).tw. (35174)
6 ((Maturit* or adult* or slow*) adj4 onset* adj4 (diabete* or diabeti* or DM)).tw. (3491)
7 ((earl* or sudden onset or child*) adj4 (diabete* or diabeti* or DM)).tw. (28251)

8 ((diabete* or diabeti* or DM) adj4 (keto* or acidi* or gastropare*)).tw. (9585)
9 ((Non-insulin* or Noninsulin*) adj4 depend* adj4 (diabete* or diabeti* or DM)).tw. (12036)
10 NIDDM.tw. (6953)
11 (insulin* adj4 independ* adj4 (diabete* or diabeti* or DM)).tw. (521)
12 or/1-11 (281088)
13 exp Infant/ or Infant Health/ or Infant Welfare/ (1227865)
14 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (1062256)
15 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (2104401)
16 Minors/ (2760)
17 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (3166183)
18 exp pediatrics/ (62618)
19 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (1174605)
20 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (2186889)
21 Puberty/ (14125)
22 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (585046)
23 Schools/ (48561)
24 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (7513)
25 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (643612)
26 ("under 16*" or "under sixteen*" or "under 18*" or "under eighteen*" or "under 25*" or "under twenty five*").ti,ab. (7588)
27 or/13-26 (6416727)
28 Hypoglycemic Agents/ (74773)
29 exp Glucagon-Like Peptide 1/ (10405)
30 ((Glucagon* adj Like adj Peptide) or recombinant glucagon*).tw. (15264)
31 (GLP* adj "1").tw. (12813)
32 GLP1*.tw. (1090)
33 Exenatide/ (2804)
34 (Exenatide* or exendin* or exenasphere* or Byetta* or Bydureon* or Saxenda*).tw. (4347)
35 (incretin mimetic* or Liraglutide* or Victoza*).tw. (3665)
36 (Dulaglutide* or Trulicity*).tw. (549)
37 (Semaglutide* or Ozempic* or Rybelsus* or wegovy*).tw. (817)
38 (Lixisenatide* or Lyxumia* or Adlyxin*).tw. (481)
39 Secretagogues/ (73)
40 (secretagog* or mitiglinide* or glufast* or starlix* or enyglid* or prandin*).tw. (9668)
41 Sodium-Glucose Transporter 2/ (1552)
42 Sodium-Glucose Transporter 2 Inhibitors/ (4775)
43 (Sodium* adj4 Glucose* adj4 Transporter* adj4 "2").tw. (2327)
44 (Sodium* adj4 Glucose* adj4 (co-transporter* or cotransporter* or co transporter*) adj4 "2").tw. (5736)
45 (SGLT* or gliflozin*).tw. (7690)

46 Canagliflozin/ (891)
47 (Canagliflozin* or Invokana* or Dapagliflozin* or andatang* or edistride* or oxra* or Forxiga* or Farxiga* or Ertugliflozin* or Steglatro* or Empagliflozin* or Jardiance* or gibtulio* or oboravo* or Glyxambi* or sulisent* or canaglu*).tw. (4478)
48 exp Sulfonylurea Compounds/tu [Therapeutic Use] (5671)
49 (Sulfonylurea* or Sulphonylurea* or sulfonurea* or sulfonyl* or sulphonurea*).tw. (18413)
50 (Gliclazide* or Bilxona* or Laaglyda* or Nazdol* or Zicron* or Diamicron* or glimicron* or glycazide* or glyclazide* or nordialex* or predian*).tw. (1489)
51 (Glimepirid* or Amaryl* or glyburide* or glucovance* or amglidia* or glibenclamide* or DiaBeta* or Glynase* or euglim* or glemax* or glimerid* or glorion* or roname* or solosa*).tw. (12309)
52 (Glipizide* or Minodiab* or Glucotrol* or aldiab* or apamid* or beapizide* or decose* or depizide* or diabes* or diasef* or dibizide* or digrin* or dipazide* or gipzide* or glibenese* or glibetin* or glibinese* or glibizide* or glican* or glidiab* or glidiazinamide* or glipicontin* or glipid* or glizide* or glucatrol* or gluco-rite* or glucorite* or glucodiab* or glucolip* or glucozide* or glupitel* or glupizide* or glutrol* or glyde* or glydiazenamide* or glydiaziamide* or glydiazinamide* or glygen* or glypizide* or glyzid* or glyzip* or melizid* or mindiab* or minidiab* or napizide* or ozidia* or pezide* or sucrazide* or sunglucon*).tw. (2341)
53 (Tolbutamid* or abemin* or aglicem* or aglycid* or arcosal* or artosin* or beglucin* or butamid* or diabecid or diaben* or diabenyl* or diabesan* or diabetamid* or diabetol* or diabeton* or metilato* or diabuton* or diasulin* or diatol* or dirastan* or dolipol* or fresan* or glicemin* or glicotron* or glyconon* or glycotron* or guabeta* or hypoglycone* or ipoglicone* or ipoglucos* or meramol* or glucosulfina* or mobenol* or antiglycemikos* or diabetal* or norboral* or neobellin* or neoinsoral* or orabet* or oresan* or orinade* or orinase* or orsinon* or osdiabet* or oterben* or pramidex* or proinsul* or rastinon* or tol-tab* or tolbugen* or tolbusal* or tolbutamate* or tolbutamin* or tolbutol* or tolbutone* or tolbutylharnstoff* or tolbutylurea* or tolglybutamide* or tolsiran* or tolubetin* or toluina* or tolumid* or toluran* or tolurast* or tolylsulfonylbutylurea* or willbutamide* or yosulan*).tw. (11391)
54 Thiazolidinediones/ (11538)
55 (Thiazolidinedione* or Glitazone*).tw. (6655)
56 Pioglitazone/ (4098)
57 (Pioglit* or cereluc* or glidipion* or paglitaz* or sepioglin* or piomed* or piozone* or pioglu* or glita or glitase* or glustin* or rosiglitazone* or avandia* or nyracta* or rezult* or rossini* or venvia* or Actos* or zactos*).tw. (11873)
58 exp Dipeptidyl-Peptidase IV Inhibitors/ or Dipeptidyl Peptidase 4/ (9217)
59 (Dipeptidyl* adj2 Peptidase* adj2 ("4" or "iv") adj Inhibitor*).tw. (3390)
60 (DPP* adj2 ("4" or "iv")).tw. (7437)
61 gliptin*.tw. (313)
62 (Saxagliptin* or Onglyza* or Komboglyze* or Qtern*).tw. (766)
63 (Vildagliptin* or vidagliptin* or equa* or jalra* or vysov* or xiliarx* or Galvus*).tw. (628742)
64 (Sitagliptin* or glactiv* or ristaben* or tesabel* or tesavel* or xelevia* or Januvia*).tw. (2655)
65 (Alogliptin* or nesina* or vipidia* or Vipdomet*).tw. (536)
66 (Linagliptin* or tradjenta* or trayenta* or Trajenta* or Jentadueto* or ondero*).tw. (920)

67 Metformin/ (16768)
68 (Metformin* or bolamyn* or diagment* or glucient* or metabet* or Glucophage* or apophage* or benofomin* or dabex* or denkaform* or deson* or dextin* or diabetase* or diabetformin* or diabetmin* or diabetosan* or diabex* or diafat* or diaformin* or diametin* or diamin* or dianben* or diformin* or dimefor* or dimethylbiguanide* or dimethyldiguanide* or eraphage or espa or euform* or fluamine* or flumamine* or fornidd* or fortamet* or glafornil* or glibudon* or glifage* or gliguanid* or glucaminol* or glucofage* or glucofago* or glucoform* or glucohexal* or glucoless* or glucomet* or glucomin* or gluconil* or glucophage* or glucostop* or glucotika* or gludepatic* or glufor* or gluformin* or glukophage* or glumeformin* or glumet* or glumetza* or glupa* or glustress* or glyciphage* or glycomet* or glycon* or glycora* or glyformin* or glymet* or haurymellin* or hipoglucin* or islotin* or jesacrin* or juformin* or lyomet* or maformin* or meglucon* or meguan* or melbin* or melformin* or mellittin* or merckformin* or mescorit* or metaformin* or metfogamma* or metfoliquid* or metforal* or metformax* or methformin* or metiguanide* or metomin* or metphormin* or miformin* or dimethylguanylgu* or dimethyldiguanide* or dimethylbiguanide* or dimethylbigu* or neoform* or riomet* or risidon* or siamformet* or siofor* or thiabet* or vimetrol* or walaphage*).tw. (74347)
69 (Competact* or actoplus* or glubrava* or metact* or piomet* or politor* or Janumet* or Eucreas* or equmet* or galvumet* or galvus* or icandra* or vysov* or zomarist* or Synjardy* or gibtulio* or jardiance* or oboravo* or Vokanamet* or invokamet* or Xigduo* or ebymect* or oxramet*).tw. (256)
70 Biguanides/ (3387)
71 Biguanide*.tw. (3236)
72 exp Glycoside Hydrolase Inhibitors/ (4600)
73 glycosid*.tw. (49316)
74 (glycosyl adj4 hydrolas*).tw. (1925)
75 ((intestinal adj4 alpha adj4 amylase adj4 inhibitor*) or (intestinal adj4 alpha-amylase adj4 inhibitor*)).tw. (15)
76 ((pancreatic adj4 alpha adj4 amylase adj4 inhibitor*) or (pancreatic adj4 alpha-amylase adj4 inhibitor*)).tw. (123)
77 ((alpha-glucosid* or alphaglucosid* or alpha-glycohydrola* or alphaglycohydrola*) adj4 inhibitor*).tw. (4374)
78 Acarbose/ (1477)
79 (Acarbos* or acarphage* or adeksa* or glumida* or glucor* or gluconase* or glucar* or glicobase* or glibose* or aglucose* or eclid * or Glucobay* or precose* or rebose* or symrose* or prandase*).tw. (6668)
80 exp Insulins/ad, tu [Administration & Dosage, Therapeutic Use] (42244)
81 exp Insulin/ad, tu [Administration & Dosage, Therapeutic Use] (39964)
82 Insulin Infusion Systems/ (6205)
83 (Insulin* adj4 (treat* or therap* or administrat* or dos* or daily or regime* or program* or human* or analogue* or biphasic* or basal* or protamine* or inject* or pen* or deliver* or device* or system* or pump* or syringe* or needle* or infusion* or tablet* or neutral* or nph)).tw. (92388)
84 (Insulin* adj4 (Intermediate* or short* or long* or ultralong* or rapid* or fast*)).tw. (30870)
85 (Actrapid* or berlinsulin* or endopancrine* or novopen* or nuralin* or umuline* or velasulin* or velosulin* or Humulin* or Hypurin*).tw. (471)

86 (afrezza* or exubera* or huminsulin* or isomarv* or solumarv* or technosphere* or novolin* or orgasulin* or umuline* or wosulin* or velosulin*).tw. (2910)
87 (Aspart* or fiasp* or kixelle * or Novolog* or Novopen* or novomix* or novorapid* or trurapi*).tw. (113751)
88 (Glulisine* or Apidra*).tw. (324)
89 (Lispro* or lyspro* or admelog* or Humalog* or liprolog* or liumjev* or lyumjev* or urli*).tw. (1282)
90 (Insulin* adj4 zinc* adj4 suspension*).tw. (95)
91 (Detemir* or Levemir*).tw. (964)
92 (Glargine* or Lantus* or Toujeo* or soliqua* or abasaglar* or abasria* or basaglar* or basalin* or basalog* or galactus* or glaricon* or glarzia* or lusduna* or optisulin* or recomulin*).tw. (3011)
93 (Degludec* or Tresiba*).tw. (731)
94 (Isophane* or Insulatard* or Insuman* or Novomix* or mixtard*).tw. (273)
95 (Fiasp* or Lyumjev* or Suliqua* or Xultophy* or NovoRapid*).tw. (97)
96 (LY2963016 or MYK-1501D or MYK1501D or Semglee*).tw. (31)
97 Biosimilar pharmaceuticals/ (3053)
98 (biosimilar* or biologics).tw. (17206)
99 Nateglinide/ (406)
100 (Meglitinide* or Repaglinide* or actulin* or enyglid* or gluconorm* or novonorm* or rapilan* or sestrine* or Nateglinide* or fastic* or glinate* or senaglinide* or trazec* or starsis*).tw. (1605)
101 or/28-100 (1118979)
102 12 and 27 and 101 (16829)
103 "Quality of Life"/ (248929)
104 quality of life.tw. (342740)
105 "Value of Life"/ (5793)
106 Quality-Adjusted Life Years/ (15067)
107 quality adjusted life.tw. (16001)
108 (qaly$ or qald$ or qale$ or qtime$).tw. (13311)
109 disability adjusted life.tw. (4581)
110 daly$.tw. (4115)
111 Health Status Indicators/ (24066)
112 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (29164)
113 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (2487)
114 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (7112)
115 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (37)
116 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (437)
117 (euroqol or euro qol or eq5d or eq 5d).tw. (14917)
118 (qol or hql or hqol or hrqol).tw. (66859)
119 (hye or hyes).tw. (75)
120 health$ year$ equivalent$.tw. (40)
121 utilit$.tw. (249944)

122 (hui or hui1 or hui2 or hui3).tw. (1843)
123 disutili$.tw. (573)
124 rosser.tw. (105)
125 quality of wellbeing.tw. (38)
126 quality of well-being.tw. (469)
127 qwb.tw. (212)
128 willingness to pay.tw. (7635)
129 standard gamble$.tw. (896)
130 time trade off.tw. (1316)
131 time tradeoff.tw. (261)
132 tto.tw. (1282)
133 or/103-132 (696842)
134 Economics/ (27463)
135 exp "Costs and Cost Analysis"/ (259935)
136 Economics, Dental/ (1920)
137 exp Economics, Hospital/ (25620)
138 exp Economics, Medical/ (14362)
139 Economics, Nursing/ (4013)
140 Economics, Pharmaceutical/ (3077)
141 Budgets/ (11639)
142 exp Models, Economic/ (16140)
143 Markov Chains/ (15788)
144 Monte Carlo Method/ (31540)
145 Decision Trees/ (12011)
146 econom$.tw. (369056)
147 cba.tw. (10876)
148 cea.tw. (25636)
149 cua.tw. (1376)
150 markov$.tw. (29402)
151 (monte adj carlo).tw. (55649)
152 (decision adj3 (tree$ or analys$)).tw. (23730)
153 (cost or costs or costing$ or costly or costed).tw. (688273)
154 (price$ or pricing$).tw. (49030)
155 budget$.tw. (33763)
156 expenditure$.tw. (65293)
157 (value adj3 (money or monetary)).tw. (2994)
158 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (4374)
159 or/134-158 (1332890)
160 Cost-Benefit Analysis/ (90565)
161 Quality-Adjusted Life Years/ (15067)
162 Markov Chains/ (15788)
163 exp Models, Economic/ (16140)
164 cost*.ti. (137179)
165 (cost* adj2 utilit*).tw. (7087)
166 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. (254790)
167 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. (42783)
168 (qualit* adj2 adjust* adj2 life*).tw. (16344)

169 QALY*.tw. (13167)
170 (incremental* adj2 cost*).tw. (15934)
171 ICER.tw. (5352)
172 utilities.tw. (8638)
173 markov*.tw. (29402)
174 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. (50965)
175 ((utility or effective*) adj2 analys*).tw. (23021)
176 (willing* adj2 pay*).tw. (8718)
177 (EQ5D* or EQ-5D*).tw. (11775)
178 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. (3332)
179 (european* adj2 quality adj3 ("5" or five)).tw. (606)
180 or/160-179 (465967)
181 133 or 159 or 180 (1965591)
182 102 and 181 (1471)
183 limit 182 to yr="2014 -Current" (740)
184 limit 183 to english language (723)
185 animals/ not humans/ (5007607)
186 184 not 185 (701)

Database name: Embase

1 diabetes mellitus/ or non insulin dependent diabetes mellitus/ (898849)
2 (Type* adj4 ("2" or "II" or two*) adj4 (diabete* or diabeti* or DM)).tw. (277255)
3 ((Type2 or T2 or TII) adj4 (diabete* or diabeti* or DM)).tw. (2065)
4 (dm2 or t2d* or mody).tw. (81470)
5 ((autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*) adj4 (diabete* or diabeti* or DM)).tw. (43566)
6 ((Maturit* or adult* or slow*) adj4 onset* adj4 (diabete* or diabeti* or DM)).tw. (4756)
7 ((earl* or sudden onset or child*) adj4 (diabete* or diabeti* or DM)).tw. (40645)
8 ((diabete* or diabeti* or DM) adj4 (keto* or acidi* or gastropare*)).tw. (14951)
9 ((Non-insulin* or Noninsulin*) adj4 depend* adj4 (diabete* or diabeti* or DM)).tw. (14076)
10 NIDDM.tw. (8075)
11 (insulin* adj4 independ* adj4 (diabete* or diabeti* or DM)).tw. (720)
12 or/1-11 (986371)
13 exp juvenile/ or Child Behavior/ or Child Welfare/ or Child Health/ or infant welfare/ or "minor (person)"/ or elementary student/ (3856354)
14 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,ad,jw. (1368102)
15 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,ad,jw. (4189264)
16 exp pediatrics/ (119983)
17 (pediatric* or paediatric* or peadiatric*).ti,ab,in,ad,jw. (1920570)
18 exp adolescence/ or exp adolescent behavior/ or adolescent health/ or high school student/ or middle school student/ (120088)

19 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,ad,jw. (776369)
20 school/ or high school/ or kindergarten/ or middle school/ or primary school/ or nursery school/ or day care/ (119265)
21 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jw. (823356)
22 ("under 16*" or "under sixteen*" or "under 18*" or "under eighteen*" or "under 25*" or "under twenty five*").ti,ab. (11793)
23 or/13-22 (7317099)
24 antidiabetic agent/ (57683)
25 exp glucagon like peptide 1 receptor agonist/ (42332)
26 ((Glucagon* adj Like adj Peptide) or recombinant glucagon*).tw. (20836)
27 (GLP* adj "1").tw. (21522)
28 GLP1*.tw. (2044)
29 exendin 4/ (11470)
30 (Exenatide* or exendin* or exenasphere* or Byetta* or Bydureon* or Saxenda*).tw. (8403)
31 (incretin mimetic* or Liraglutide* or Victoza*).tw. (7255)
32 (Dulaglutide* or Trulicity*).tw. (1242)
33 (Semaglutide* or Ozempic* or Rybelsus* or wegovy*).tw. (1521)
34 (Lixisenatide* or Lyxumia* or Adlyxin*).tw. (942)
35 secretagogue/ (371)
36 (secretagog* or mitiglinide* or glufast* or starlix* or enyglid* or prandin*).tw. (11736)
37 sodium glucose cotransporter 2 inhibitor/ (9056)
38 sodium glucose cotransporter 2/ (4134)
39 (Sodium* adj4 Glucose* adj4 Transporter* adj4 "2").tw. (3542)
40 (Sodium* adj4 Glucose* adj4 (co-transporter* or cotransporter* or co transporter*) adj4 "2").tw. (7966)
41 (SGLT* or gliflozin*).tw. (12697)
42 canagliflozin/ (4585)
43 (Canagliflozin* or Invokana* or Dapagliflozin* or andatang* or edistride* or oxra* or Forxiga* or Farxiga* or Ertugliflozin* or Steglatro* or Empagliflozin* or Jardiance* or gibtulio* or oboravo* or Glyxambi* or sulisent* or canaglu*).tw. (8541)
44 sulfonylurea/dt [Drug Therapy] (9698)
45 exp sulfonylurea derivative/ (68041)
46 (Sulfonylurea* or Sulphonylurea* or sulfonurea* or sulfonyl* or sulphonurea*).tw. (24392)
47 (Gliclazide* or Bilxona* or Laaglyda* or Nazdol* or Zicron* or Diamicron* or glimicron* or glycazide* or glyclazide* or nordialex* or predian*).tw. (3019)
48 (Glimepirid* or Amaryl* or glyburide* or glucovance* or amglidia* or glibenclamide* or DiaBeta* or Glynase* or euglim* or glemax* or glimerid* or glorion* or roname* or solosa*).tw. (18107)
49 (Glipizide* or Minodiab* or Glucotrol* or aldiab* or apamid* or beapizide* or decose* or depizide* or diabes* or diasef* or dibizide* or digrin* or dipazide* or gipzide* or glibenese* or glibetin* or glibinese* or glibizide* or glican* or glidiab* or glidiazinamide* or glipicontin* or glipid* or glizide* or glucatrol* or gluco-rite* or glucorite* or glucodiab* or glucolip* or glucozide* or glupitel* or glupizide* or glutrol*

or glyde* or glydiazenamide* or glydiaziamide* or glydiazinamide* or glygen* or glypizide* or glyzid* or glyzip* or melizid* or mindiab* or minidiab* or napizide* or ozidia* or pezide* or sucrazide* or sunglucon*).tw. (4128)
50 (Tolbutamid* or abemin* or aglicem* or aglycid* or arcosal* or artosin* or beglucin* or butamid* or diabecid or diaben* or diabenyl* or diabesan* or diabetamid* or diabetol* or diabeton* or metilato* or diabuton* or diasulin* or diatol* or dirastan* or dolipol* or fresan* or glicemin* or glicotron* or glyconon* or glycotron* or guabeta* or hypoglycone* or ipoglicone* or ipoglucos* or meramol* or glucosulfina* or mobenol* or antiglycemikos* or diabetal* or norboral* or neobellin* or neoinsoral* or orabet* or oresan* or orinade* or orinase* or orsinon* or osdiabet* or oterben* or pramidex* or proinsul* or rastinon* or tol-tab* or tolbugen* or tolbusal* or tolbutamate* or tolbutamin* or tolbutol* or tolbutone* or tolbutylharnstoff* or tolbutylurea* or tolglybutamide* or tolsiran* or tolubetin* or toluina* or tolumid* or toluran* or tolurast* or tolylsulfonylbutylurea* or willbutamide* or yosulan*).tw. (15570)
51 2,4 thiazolidinedione/ or 2,4 thiazolidinedione derivative/ (14332)
52 (Thiazolidin* or Glitazone*).tw. (13224)
53 exp glitazone derivative/ (40326)
54 (Pioglit* or cereluc* or glidipion* or paglitaz* or sepioglin* or piomed* or piozone* or pioglu* or glita or glitase* or glustin* or rosiglitazone* or avandia* or nyracta* or rezult* or rossini* or venvia* or Actos* or zactos*).tw. (17765)
55 dipeptidyl peptidase iv/ or exp dipeptidyl peptidase iv inhibitor/ (30769)
56 (Dipeptidyl* adj2 Peptidase* adj2 ("4" or "iv") adj Inhibitor*).tw. (4655)
57 (DPP* adj2 ("4" or "iv")).tw. (11351)
58 gliptin*.tw. (542)
59 (Saxagliptin* or Onglyza* or Komboglyze* or Qtern*).tw. (1649)
60 (Vildagliptin* or vidagliptin* or equa* or jalra* or vysov* or xiliarx* or Galvus*).tw. (736105)
61 (Sitagliptin* or glactiv* or ristaben* or tesabel* or tesavel* or xelevia* or Januvia*).tw. (5528)
62 (Alogliptin* or nesina* or vipidia* or Vipdomet*).tw. (931)
63 (Linagliptin* or tradjenta* or trayenta* or Trajenta* or Jentadueto* or ondero*).tw. (1864)
64 metformin/ (77843)
65 (Metformin* or bolamyn* or diagment* or glucient* or metabet* or Glucophage* or apophage* or benofomin* or dabex* or denkaform* or deson* or dextin* or diabetase* or diabetformin* or diabetmin* or diabetosan* or diabex* or diafat* or diaformin* or diametin* or diamin* or dianben* or diformin* or dimefor* or dimethylbiguanide* or dimethyldiguanide* or eraphage or espa or euform* or fluamine* or flumamine* or fornidd* or fortamet* or glafornil* or glibudon* or glifage* or gliguanid* or glucaminol* or glucofage* or glucofago* or glucoform* or glucohexal* or glucoless* or glucomet* or glucomin* or gluconil* or glucophage* or glucostop* or glucotika* or gludepatic* or glufor* or gluformin* or glukophage* or glumeformin* or glumet* or glumetza* or glupa* or glustress* or glyciphage* or glycomet* or glycon* or glycora* or glyformin* or glymet* or haurymellin* or hipoglucin* or islotin* or jesacrin* or juformin* or lyomet* or maformin* or meglucon* or meguan* or melbin* or melformin* or mellittin* or merckformin* or mescorit* or metaformin* or metfogamma* or metfoliquid* or metforal* or metformax* or methformin* or metiguanide* or metomin* or metphormin* or miformin* or dimethylguanylgu* or dimethyldiguanide* or

dimethylbiguanide* or dimethylbigu* or neoform* or riomet* or risidon* or siamformet* or siofor* or thiabet* or vimetrol* or walaphage*).tw. (100536)
66 (Competact* or actoplus* or glubrava* or metact* or piomet* or politor* or Janumet* or Eucreas* or equmet* or galvumet* or icandra* or vysov* or zomarist* or Synjardy* or gibtulio* or jardiance* or oboravo* or Vokanamet* or invokamet* or Xigduo* or ebymect* or oxramet*).tw. (599)
67 exp biguanide derivative/ (114522)
68 Biguanide*.tw. (4190)
69 exp glycosidase inhibitor/ (37751)
70 glycosid*.tw. (59717)
71 (glycosyl adj4 hydrolas*).tw. (2000)
72 ((intestinal adj4 alpha adj4 amylase adj4 inhibitor*) or (intestinal adj4 alpha-amylase adj4 inhibitor*)).tw. (24)
73 ((pancreatic adj4 alpha adj4 amylase adj4 inhibitor*) or (pancreatic adj4 alpha-amylase adj4 inhibitor*)).tw. (144)
74 ((alpha-glucosid* or alphaglucosid* or alpha-glycohydrola* or alphaglycohydrola*) adj4 inhibitor*).tw. (5637)
75 exp alpha glucosidase inhibitor/ (18109)
76 (Acarbos* or acarphage* or adeksa* or glumida* or glucor* or gluconase* or glucar* or glicobase* or glibose* or aglucose* or eclid * or Glucobay* or precose* or rebose* or symrose* or prandase*).tw. (9648)
77 exp insulin derivative/ad, do, dt [Drug Administration, Drug Dose, Drug Therapy] (82888)
78 insulin infusion/ (9082)
79 (Insulin* adj4 (treat* or therap* or administrat* or dos* or daily or regime* or program* or human* or analogue* or biphasic* or basal* or protamine* or inject* or pen* or deliver* or device* or system* or pump* or syringe* or needle* or infusion* or tablet* or neutral* or nph)).tw. (133827)
80 (Insulin* adj4 (Intermediate* or short* or long* or ultralong* or rapid* or fast*)).tw. (45900)
81 (Actrapid* or berlinsulin* or endopancrine* or novopen* or nuralin* or umuline* or velasulin* or velosulin* or Humulin* or Hypurin*).tw. (5801)
82 (afrezza* or exubera* or huminsulin* or isomarv* or solumarv* or technosphere* or novolin* or orgasulin* or umuline* or wosulin* or velosulin*).tw. (5689)
83 (Aspart* or fiasp* or kixelle * or Novolog* or Novopen* or novomix* or novorapid* or trurapi*).tw. (135070)
84 (Glulisine* or Apidra*).tw. (1053)
85 (Lispro* or lyspro* or admelog* or Humalog* or liprolog* or liumjev* or lyumjev* or urli*).tw. (3662)
86 (Insulin* adj4 zinc* adj4 suspension*).tw. (57)
87 (Detemir* or Levemir*).tw. (2579)
88 (Glargine* or Lantus* or Toujeo* or soliqua* or abasaglar* or abasria* or basaglar* or basalin* or basalog* or galactus* or glaricon* or glarzia* or lusduna* or optisulin* or recomulin*).tw. (7693)
89 (Degludec* or Tresiba*).tw. (1783)
90 (Isophane* or Insulatard* or Insuman* or Novomix* or mixtard*).tw. (1584)
91 (Fiasp* or Lyumjev* or Suliqua* or Xultophy* or NovoRapid*).tw. (1163)
92 (LY2963016 or MYK-1501D or MYK1501D or Semglee*).tw. (85)
93 biosimilar agent/ (6158)

94 (biosimilar* or biologics).tw. (36497)
95 nateglinide/ (2753)
96 meglitinide/ (2148)
97 repaglinide/ (4168)
98 (Meglitinide* or Repaglinide* or actulin* or enyglid* or gluconorm* or novonorm* or rapilan* or sestrine* or Nateglinide* or fastic* or glinate* or senaglinide* or trazec* or starsis*).tw. (2655)
99 or/24-98 (1519208)
100 12 and 23 and 99 (41110)
101 "Quality of Life"/ (569757)
102 Quality Adjusted Life Year/ (32389)
103 Quality of Life Index/ (3059)
104 Short Form 36/ (35873)
105 Health Status/ (143779)
106 quality of life.tw. (538667)
107 quality adjusted life.tw. (24268)
108 (qaly$ or qald$ or qale$ or qtime$).tw. (24615)
109 disability adjusted life.tw. (5505)
110 daly$.tw. (5308)
111 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (47251)
112 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (2780)
113 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (11356)
114 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (66)
115 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (501)
116 (euroqol or euro qol or eq5d or eq 5d).tw. (27043)
117 (qol or hql or hqol or hrqol).tw. (119698)
118 (hye or hyes).tw. (152)
119 health$ year$ equivalent$.tw. (41)
120 utilit$.tw. (347226)
121 (hui or hui1 or hui2 or hui3).tw. (2843)
122 disutili$.tw. (1126)
123 rosser.tw. (136)
124 quality of wellbeing.tw. (65)
125 quality of well-being.tw. (547)
126 qwb.tw. (264)
127 willingness to pay.tw. (11546)
128 standard gamble$.tw. (1169)
129 time trade off.tw. (1944)
130 time tradeoff.tw. (309)
131 tto.tw. (2028)
132 or/101-131 (1191010)
133 exp Health Economics/ (976961)
134 exp "Health Care Cost"/ (324996)

135 exp Pharmacoeconomics/ (222145)
136 Monte Carlo Method/ (47262)
137 Decision Tree/ (18284)
138 econom$.tw. (452195)
139 cba.tw. (13689)
140 cea.tw. (39205)
141 cua.tw. (1735)
142 markov$.tw. (36647)
143 (monte adj carlo).tw. (57032)
144 (decision adj3 (tree$ or analys$)).tw. (32457)
145 (cost or costs or costing$ or costly or costed).tw. (919170)
146 (price$ or pricing$).tw. (67546)
147 budget$.tw. (44417)
148 expenditure$.tw. (85602)
149 (value adj3 (money or monetary)).tw. (4017)
150 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (9335)
151 or/133-150 (2090163)
152 cost utility analysis/ (11353)
153 quality adjusted life year/ (32389)
154 cost*.ti. (183095)
155 (cost* adj2 utilit*).tw. (11604)
156 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. (353717)
157 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. (60396)
158 (qualit* adj2 adjust* adj2 life*).tw. (24862)
159 QALY*.tw. (24363)
160 (incremental* adj2 cost*).tw. (26168)
161 ICER.tw. (11641)
162 utilities.tw. (13874)
163 markov*.tw. (36647)
164 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. (66759)
165 ((utility or effective*) adj2 analys*).tw. (34451)
166 (willing* adj2 pay*).tw. (13071)
167 (EQ5D* or EQ-5D*).tw. (22866)
168 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. (4490)
169 (european* adj2 quality adj3 ("5" or five)).tw. (836)
170 or/152-169 (583415)
171 132 or 151 or 170 (3132294)
172 100 and 171 (5179)
173 (conference abstract* or conference review or conference paper).db,pt. (5304298)
174 172 not 173 (3452)
175 limit 174 to yr="2014 -Current" (1764)
176 limit 175 to english language (1712)

Database name: EconLit

1 [exp Diabetes Mellitus, Type 2/] (0)
2 (Type* adj4 ("2" or "II" or two*) adj4 (diabete* or diabeti* or DM)).tw. (129)
3 ((Type2 or T2 or TII) adj4 (diabete* or diabeti* or DM)).tw. (1)
4 (dm2 or t2d* or mody).tw. (54)
5 ((autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*) adj4 (diabete* or diabeti* or DM)).tw. (5)
6 ((Maturit* or adult* or slow*) adj4 onset* adj4 (diabete* or diabeti* or DM)).tw. (0)
7 ((earl* or sudden onset or child*) adj4 (diabete* or diabeti* or DM)).tw. (17)
8 ((diabete* or diabeti* or DM) adj4 (keto* or acidi* or gastropare*)).tw. (1)
9 ((Non-insulin* or Noninsulin*) adj4 depend* adj4 (diabete* or diabeti* or DM)).tw. (2)
10 NIDDM.tw. (3)
11 (insulin* adj4 independ* adj4 (diabete* or diabeti* or DM)).tw. (0)
12 or/1-11 (186)
13 [exp Infant/ or Infant Health/ or Infant Welfare/] (0)
14 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (6641)
15 [exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/] (0)
16 [Minors/] (0)
17 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (55277)
18 [exp pediatrics/] (0)
19 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (210)
20 [Adolescent/ or Adolescent Behavior/ or Adolescent Health/] (0)
21 [Puberty/] (0)
22 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (10603)
23 [Schools/] (0)
24 [Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/] (0)
25 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (57217)
26 ("under 16*" or "under sixteen*" or "under 18*" or "under eighteen*" or "under 25*" or "under twenty five*").ti,ab. (83)
27 or/13-26 (109915)
28 12 and 27 (24)
29 limit 28 to yr="2014 -Current" (14)

Database name: EED

1	MeSH DESCRIPTOR Diabetes Mellitus, Type 2 EXPLODE ALL TREES	1217
2	((Type* near4 ("2" or "II" or two*) near4 (diabete* or diabeti* or DM)))	1351
3	(((Type2 or T2 or TII) near4 (diabete* or diabeti* or DM)))	4

4	((dm2 or t2d* or mody))	52
5	(((autoimmun* or "auto immun*" or brittle or labile or "insulin depend*" or "insulin deficien*") near4 (diabete* or diabeti* or DM)))	130
6	(((Maturit* or adult* or slow*) near4 onset* near4 (diabete* or diabeti* or DM)))	4
7	(((earl* or "sudden onset" or child*) near4 (diabete* or diabeti* or DM)))	141
8	(((diabete* or diabeti* or DM) near4 (keto* or acidi* or gastropare*)))	34
9	((("Non-insulin*" or Noninsulin*) near4 depend* near4 (diabete* or diabeti* or DM)))	59
10	(NIDDM)	32
11	((insulin* near4 independ* near4 (diabete* or diabeti* or DM)))	0
12	(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11)	1847
13	MeSH DESCRIPTOR Infant EXPLODE ALL TREES	2964
14	MeSH DESCRIPTOR Infant Health	0
15	((prematur* or "pre-matur*" or preterm* or "pre-term*" or infan* or newborn* or "new-born*" or perinat* or "peri-nat*" or neonat* or "neo-nat*" or baby* or babies or toddler*))	5510
16	MeSH DESCRIPTOR Child EXPLODE ALL TREES	4935
17	MeSH DESCRIPTOR Child Behavior EXPLODE ALL TREES	64
18	MeSH DESCRIPTOR Child Health	2
19	MeSH DESCRIPTOR Child Welfare	80
20	MeSH DESCRIPTOR Minors	2
21	((child* or minor or minors or boy* or girl* or kid or kids or young*))	13575
22	MeSH DESCRIPTOR Pediatrics EXPLODE ALL TREES	119
23	((pediatric* or paediatric* or peadiatric*))	2842
24	MeSH DESCRIPTOR Adolescent	4594
25	MeSH DESCRIPTOR Adolescent Behavior	94
26	MeSH DESCRIPTOR Adolescent Health	0
27	MeSH DESCRIPTOR Puberty	3

28	((adolescen* or pubescen* or prepubescen* or "pre-pubescen*" or pubert* or prepubert* or pre-pubert* or teen* or preteen* or "pre-teen*" or juvenil* or youth* or "under*age*"))	5621
29	MeSH DESCRIPTOR Schools	168
30	MeSH DESCRIPTOR Child Day Care Centers	12
31	MeSH DESCRIPTOR Nurseries, Infant EXPLODE ALL TREES	0
32	MeSH DESCRIPTOR Schools, Nursery	3
33	(("pre-school*" or preschool* or kindergar* or daycare or "day-care" or nurser* or school* or pupil* or student*))	4454
34	(("under 16*" or "under sixteen*" or "under 18*" or "under eighteen*" or "under 25*" or "under twenty five*"))	169
35	#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 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34	18464
36	#12 AND #35	363
37	(#12 AND #35) FROM 2014 TO 2022 (4 EED)	27

Database name: HTA

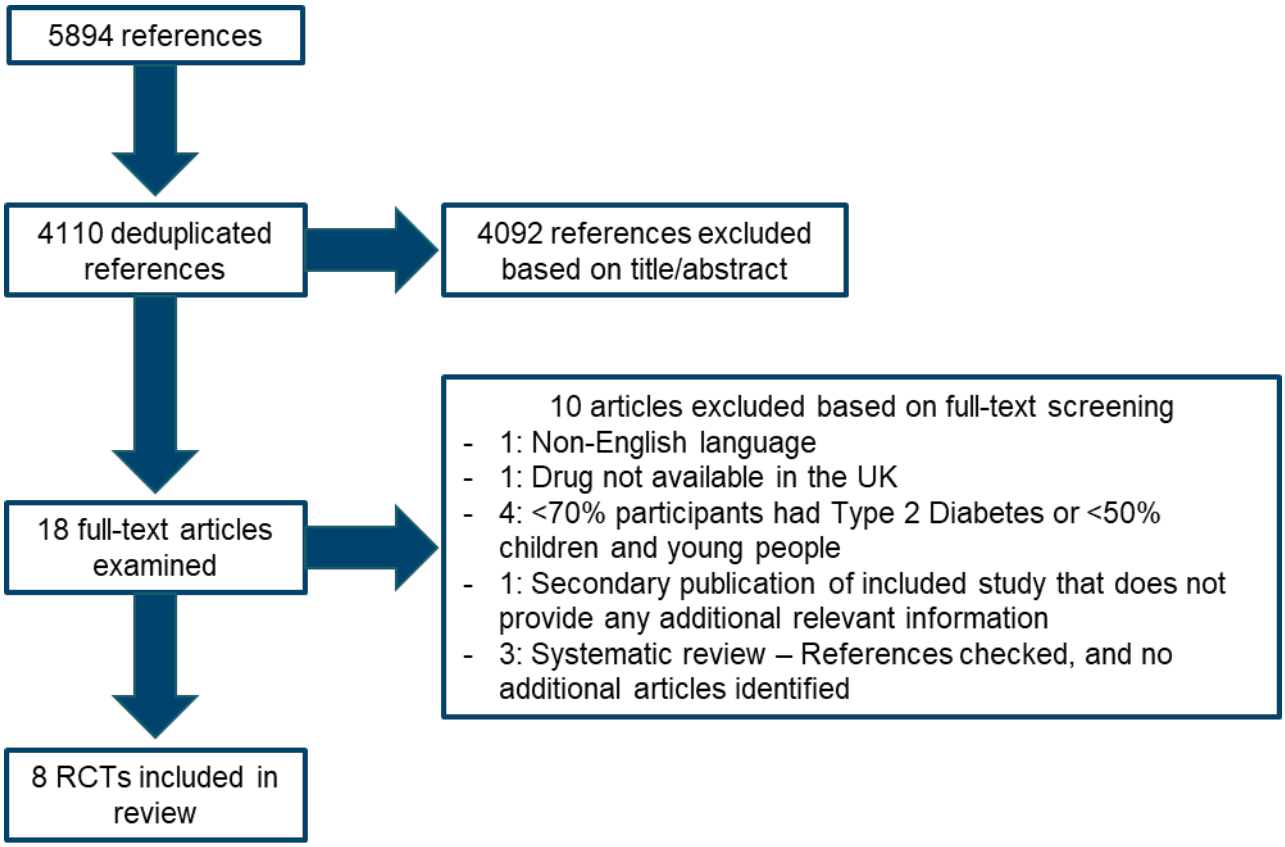
1	MeSH DESCRIPTOR Diabetes Mellitus, Type 2 EXPLODE ALL TREES	1217
2	((Type* near4 ("2" or "II" or two*) near4 (diabete* or diabeti* or DM)))	1351
3	(((Type2 or T2 or TII) near4 (diabete* or diabeti* or DM)))	4
4	((dm2 or t2d* or mody))	52
5	(((autoimmun* or "auto immun*" or brittle or labile or "insulin depend*" or "insulin deficien*") near4 (diabete* or diabeti* or DM)))	130
6	(((Maturit* or adult* or slow*) near4 onset* near4 (diabete* or diabeti* or DM)))	4
7	(((earl* or "sudden onset" or child*) near4 (diabete* or diabeti* or DM)))	141
8	(((diabete* or diabeti* or DM) near4 (keto* or acidi* or gastropare*)))	34
9	((("Non-insulin*" or Noninsulin*) near4 depend* near4 (diabete* or diabeti* or DM)))	59
10	(NIDDM)	32

11	((insulin* near4 independ* near4 (diabete* or diabeti* or DM)))	0
12	(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11)	1847
13	MeSH DESCRIPTOR Infant EXPLODE ALL TREES	2964
14	MeSH DESCRIPTOR Infant Health	0
15	((prematur* or "pre-matur*" or preterm* or "pre-term*" or infan* or newborn* or "new-born*" or perinat* or "peri-nat*" or neonat* or "neo-nat*" or baby* or babies or toddler*))	5510
16	MeSH DESCRIPTOR Child EXPLODE ALL TREES	4935
17	MeSH DESCRIPTOR Child Behavior EXPLODE ALL TREES	64
18	MeSH DESCRIPTOR Child Health	2
19	MeSH DESCRIPTOR Child Welfare	80
20	MeSH DESCRIPTOR Minors	2
21	((child* or minor or minors or boy* or girl* or kid or kids or young*))	13575
22	MeSH DESCRIPTOR Pediatrics EXPLODE ALL TREES	119
23	((pediatric* or paediatric* or peadiatric*))	2842
24	MeSH DESCRIPTOR Adolescent	4594
25	MeSH DESCRIPTOR Adolescent Behavior	94
26	MeSH DESCRIPTOR Adolescent Health	0
27	MeSH DESCRIPTOR Puberty	3
28	((adolescen* or pubescen* or prepubescen* or "pre-pubescen*" or pubert* or prepubert* or pre-pubert* or teen* or preteen* or "pre-teen*" or juvenil* or youth* or "under*age*"))	5621
29	MeSH DESCRIPTOR Schools	168
30	MeSH DESCRIPTOR Child Day Care Centers	12
31	MeSH DESCRIPTOR Nurseries, Infant EXPLODE ALL TREES	0
32	MeSH DESCRIPTOR Schools, Nursery	3
33	(("pre-school*" or preschool* or kindergar* or daycare or "day-care" or nurser* or school* or pupil* or student*))	4454
34	(("under 16*" or "under sixteen*" or "under 18*" or "under eighteen*" or "under 25*" or "under twenty five*"))	169

35	#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 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34	18464
36	#12 AND #35	363
37	(#12 AND #35) FROM 2014 TO 2022 (8 HTA)	27

Appendix C – Effectiveness evidence study selection

Figure 1: PRISMA flow chart



Appendix D – Effectiveness evidence

Evidence tables

Arslanian 2022

Bibliographic Reference	Arslanian, Silva A; Hannon, Tamara; Zeitler, Philip; Chao, Lily C; Boucher-Berry, Claudia; Barrientos-Perez, Margarita; Bismuth, Elise; Dib, Sergio; Cho, Jang Ik; Cox, David; AWARD-PEDS, Investigators; Once-Weekly Dulaglutide for the Treatment of Youths with Type 2 Diabetes.; The New England journal of medicine; 2022; vol. 387 (no. 5); 433-443

Study details

Study type	Phase 3 Randomised controlled trial (RCT)
Blinding	Double blind
Trial registration number and/or trial name	NCT02963766
Number of participants	N=154
Duration of trial	26 weeks
Study setting	Various
Study location	Multisite (46 centres in 9 countries)
Study dates	12/2016 to 12/2020
Inclusion criteria	• Aged 10 to <18 years-old with Type 2 Diabetes • BMI>85th percentile for age and sex in participant's country or region • Weight ≥50 kg • HbA1c >6.5-≤11% if taking metformin with or without basal insulin therapy or >6.5% - ≤9% if treated with diet and exercise only • Stable metformin or insulin dose, if applicable, ≥8 weeks before screening
Exclusion criteria	• Type 1 diabetes or positive antibodies against insulinoma-associated protein 2 or 65-kD isoform of glutamic acid decarboxylase • Use of any antidiabetic agents other than metformin or basal insulin within 3-mo of screening • History of pancreatitis • Serum calcitonin level ≥20 pg/ml • Personal or family history of multiple endocrine neoplasia type 2A or type 2B • Thyroid C-cell hyperplasia • Medullary thyroid carcinoma
General details about study	Stratified randomisation, 1:1:1 ratio according to glycated haemoglobin level<8% or ≥8%, metformin use, and insulin use. 78% of participants were receiving metformin with or without basal insulin at baseline. Reports baseline characteristics balanced across groups.
Intervention(s)	Subcutaneous dulaglutide injection 0.75 mg or 1.5 mg, once weekly, via single-use, single-dose pen for 26 weeks. Participants in 1.5 mg group received 0.75 mg for 4

	weeks and escalated if tolerated. Trial also included subsequent 26-weeek open-label extension period in which participants in dulaglutide group continued with relevant doses and placebo group received dulaglutide 0.75 mg. Diet and exercise counselling provided at each visit.
Comparator	Visually identical placebo via single-use, single-dose pen.
Other publications associated with this study included in review	None
Secondary publication of another included study- see primary study for details	No
Sources of funding	Supported by Eli Lilly
Outcome measures	• Glycated haemoglobin (HbA1c) level • Glucose level • BMI z-score • Participants needing rescue medication in form of insulin • Serious adverse events • Severe hypoglycaemic episode • Pancreatitis • Other gastrointestinal symptoms

Study arms

Dulaglutide 0.75 mg (N = 51)

Subcutaneous dulaglutide injection 0.75 mg per week

Dulaglutide 1.5 mg (N = 52)

Subcutaneous dulaglutide injection 1.5 mg per week

Placebo (N = 51)

Matching placebo

Characteristics

Study-level characteristics

Characteristic	Study (N = 154)
% Female Sample size	n = 110 ; % = 71
Mean age (SD) (years) Mean (SD)	14.5 (2)
BMI (kg/m2) Mean (SD)	34.1 (8.8)

Characteristic	Study (N = 154)
American Indian or Alaska Native Sample size	n = 16 ; % = 10
Asian Sample size	n = 19 ; % = 12
Black Sample size	n = 23 ; % = 15
Native Hawaiian or other Pacific Islander Sample size	n = 1 ; % = 1
Multiple Sample size	n = 7 ; % = 5
White Sample size	n = 84 ; % = 55
Missing data Sample size	n = 4 ; % = 3
Duration of Type 2 Diabetes (years) Mean (SD)	2 (1.7)
Glycated haemoglobin (HbA1c) (%) Mean (SD)	8.1 (1.3)
Fasting Plasma Glucose (FPG) (mmol/L) Mean (SD)	8.7 (3.4)
Metformin use/dose at baseline (Number of participants, %) Sample size	n = 136 ; % = 78
Metformin only Sample size	n = 97 ; % = 63
Metformin plus basal insulin Sample size	n = 39 ; % = 25
Insulin use at baseline (Number of participants, %) Sample size	n = 43 ; % = 25

Critical appraisal

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns (No information provided regarding method of randomisation nor allocation concealment.)

Cochrane Risk of Bias Tool 2.0		
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low (Double-blind trial with ITT analysis)
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low (Double-blind trial with high completion rate.)
Domain 3: Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low (ITT analysis with missing data accounted for using multiple imputation.)
Domain 4: Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low/Some concerns (Majority of outcomes laboratory assessed, but some concerns for participant-reported outcomes.)
Domain 5 Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low (Main outcomes reported in line with trial protocol.)
Overall bias	Risk of bias judgement	Moderate (Some concerns regarding randomisation process and allocation concealment.)

Cochrane Risk of Bias Tool 2.0		
Directness	Overall Directness	Partially applicable (All participants under 18-years and had type 2 diabetes. However, only 78% receiving metformin with or without basal insulin.)

Jalaludin 2022

Bibliographic Reference Jalaludin, Muhammad Yazid; Deeb, Asma; Zeitler, Philip; Garcia, Raymundo; Newfield, Ron S; Samoilova, Yulia; Rosario, Carmen A; Shehadeh, Naim; Saha, Chandan K; Zhang, Yilong; Zilli, Martina; Scherer, Lynn W; Lam, Raymond L H; Golm, Gregory T; Engel, Samuel S; Kaufman, Keith D; Shankar, R Ravi; Efficacy and safety of the addition of sitagliptin to treatment of youth with type 2 diabetes and inadequate glycemic control on metformin without or with insulin.; Pediatric diabetes; 2022; vol. 23 (no. 2); 183-193

Study details

Study type	Phase 3 Randomised controlled trial (RCT)
Blinding	Double blind
Trial registration number and/or trial name	NCT01472367 and NCT01760447
Number of participants	N=220
Duration of trial	54 weeks (20 weeks rescue period, 34 weeks intensification period)
Study setting	Various
Study location	Multisite (7 countries Dominican Republic, Israel, Malaysia, Mexico, Russia, United Arab Emirates, USA)
Study dates	12/2011 to 09/2019 (NCT01472367) 02/2013 to 09/2019 (NCT01760447)
Inclusion criteria	• Aged 10-17 years-old with Type 2 Diabetes • HbA1c ≥6.5% - ≤ 10.0% if on ≥1500 mg/day metformin only for ≥12 weeks, or ≥ 7.0% - ≤ 10.0% if on any type of insulin therapy in addition to metformin for ≥12 weeks • BMI ≥85th percentile at screening or a history of being overweight or obese at T2D diagnosis • Fasting C-peptide >0.6 ng/ml if on insulin or had a duration of diabetes <1 year, and FPG<13.3 mmol/L at randomisation

Exclusion criteria	• History of Type 1 Diabetes • Autoimmune diabetes (or a positive antibody screen for anti-GAD or ICA-512) at diagnosis or disorders other than Type 2 Diabetes known to affect glucose tolerance
General details about study	Pooled analysis of two placebo-controlled studies on addition of sitagliptin to metformin (with or without insulin). Stratified randomisation according to metformin use and insulin use at screening. Participants on stable doses of metformin ≥1000 mg/day to <1500 mg/day (with or without insulin) for ≥12 weeks permitted to participate with documentation of intolerance to higher doses. During first 20 weeks, rescue medication in form of insulin permitted if progressively stricter glycaemic rescue fasting plasma glucose (FPG) thresholds exceeded and not already on in it. Participants on insulin at start of study increased background insulin dose by >15% if rescue thresholds met. From week 20 to week 54, participants continued in assigned group and insulin glargine initiated or up-titrated background insulin by >15% if fingerstick HbA1c >7.5% and fasting FPG>130 mg/dl (7.2 mmol/L). Participants discontinued study medication if they could not or would not up-titrate background insulin or initiate insulin when rescue thresholds met. During participant-blind placebo run-in period for both trials, and reinforced throughout trial duration, parents/guardians educated in pathophysiology and treatment of Type 2 Diabetes using materials adapted for use with young people with Type 2 Diabetes from the Lifestyle Intervention arm of the TODAY study (including nutritional advice and exercise recommendations). NCT01472367: One-week participant-blind run-in period in which participants received metformin dose adjusted concordant with doses of metformin in fixed-dose combination, 500 mg, 850 mg, 1000 mg, as well as placebo to JANUMET dose. NCT01760447: One-week participant-blind run-in period in which participants received metformin XR at doses concordant with metformin XR doses in fixed-dose combination, 500 mg, 850 mg, 1000 mg, as well as placebo to JANUMET XR dose. Reports baseline characteristics similar between groups in both trials.
Intervention(s)	NCT01472367: Fixed-dose combination of Sitagliptin 50 mg and immediate-release metformin (JANUMET, MK-0431A), twice daily, plus placebo to immediate-release metformin. NCT01760447: Fixed-dose combination of Sitagliptin 100 mg and extended-release metformin (JANUMET XR, MK-0431A XR), once daily, plus placebo to extended-release metformin.
Comparator	NCT01472367: Metformin and Placebo to JANUMET NCT01760447: Metformin XR and Placebo to JANUMET XR
Other publications associated with this study included in review	None
Secondary publication of another included study- see primary study for details	No
Sources of funding	Funded by Merck Sharp & Dohme Corp., subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA

Outcome measures	• Glycated haemoglobin (HbA1c) level • Glucose level • BMI z-score (Only reports mean BMI, kg/m2). • Participants needing rescue medication in form of insulin • Serious adverse events • Severe hypoglycaemic episode • Other gastrointestinal symptoms

Study arms

Sitagliptin 100 mg/Metformin FDC (N = 107)

Oral sitagliptin 100 mg per day/Metformin FDC

Metformin (N = 113)

Characteristics

Study-level characteristics

Characteristic	Study (N = 220)
% Female Sample size	n = 145 ; % = 66
Mean age (SD) (years) Mean (SD)	14.4 (1.9)
BMI (kg/m2) Mean (SD)	30.9 (8.3)
American Indian or Alaska Native Sample size	n = 13 ; % = 6
Asian Sample size	n = 64 ; % = 29
Black or African American Sample size	n = 10 ; % = 4.5
Hispanic or Latino Sample size	n = 77 ; % = 35
Multiple Sample size	n = 35 ; % = 16
Native Hawaiian or other Pacific Islander Sample size	n = 2 ; % = 1
White Sample size	n = 96 ; % = 44
Duration of Type 2 Diabetes (years) Mean (SD)	2.2 (1.6)
Glycated haemoglobin (HbA1c) (%) Mean (SD)	8.1 (1.1)
Fasting Plasma Glucose (FPG) (mmol/L) Mean (SD)	8.2 (2.8)
Metformin use/dose at baseline (Number of participants, %) Sample size	n = 220 ; % = 100
Insulin use at baseline (Number of participants, %) Sample size	n = 33 ; % = 15

Critical appraisal

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns (No information about randomisation and allocation concealment, and less 10-<15 year-olds in sitagliptin group compared to metformin (39.3% vs 49.6%)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low (Double-blind trial with ITT analysis.)
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low (High rate of adherence to interventions)
Domain 3: Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns (~92% and ~87% completed 20 and 54 weeks trial on intervention, high proportion of missing data due to receipt of rescue therapy during trial.)
Domain 4: Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low (Majority of outcomes were laboratory measures but some concerns for participant-reported outcomes.)

Cochrane Risk of Bias Tool 2.0		
Domain 5 Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low (Results reported in line with trial protocol.)
Overall bias	Risk of bias judgement	Some concerns (Some concerns regarding randomisation process and missing data in trial.)
Directness	Overall Directness	Directly applicable (All participants were 10-17 years-old, had Type 2 Diabetes and had inadequate glycaemic control on metformin with or without insulin.)

Laffel, 2023

Bibliographic Reference Laffel, Lori M; Danne, Thomas; Klingensmith, Georgeanna J; Tamborlane, William V; Willi, Steven; Zeitler, Philip; Neubacher, Dietmar; Marquard, Jan; Efficacy and safety of the SGLT2 inhibitor empagliflozin versus placebo and the DPP-4 inhibitor linagliptin versus placebo in young people with type 2 diabetes (DINAMO): a multicentre, randomised, double-blind, parallel group, phase 3 trial.; The lancet. Diabetes & endocrinology; 2023; vol. 11 (no. 3); 169-181

Study details

Study type	Phase III Randomised controlled trial (RCT)
Trial registration number and/or trial name	NCT03429543/DINAMO
Number of participants	N=158
Duration of trial	52 weeks (first 26 weeks compared to placebo)
Study setting	Various
Study location	Multisite (108 centres in 13 countries)
Study dates	April 2018 to May 2022

Inclusion criteria	• Aged 10–17 years at randomisation • Women of child-bearing potential ready and able to use effective methods of birth control (low failure rate <1% a year) • Type 2 diabetes for at least 8 weeks before screening • HbA1c level 6·5%-10·5% (48–91 mmol/mol) at screening • BMI≥85th percentile at entry into run-in • Treated with diet and exercise plus ≥metformin 1000 mg/day (or up to maximal tolerated dose) at stable dose for 8 weeks prior to visit 2 or not tolerating metformin AND/OR diet and exercise and stable basal/multiple dose insulin therapy • Negative test for both insulinoma-associated antigen-2 and glutamic acid decarboxylase autoantibodies (measured by central laboratory at first visit)
Exclusion criteria	• Any antidiabetic medication (except metformin or insulin background therapy) continued during the study within 8 weeks before first visit • Any history of acute metabolic decompensation (eg. DKA) within 8 weeks prior to visit 1A and up to randomisation • History of pancreatitis • Pregnancy • Metabolic bone disease • Gastrointestinal disorder that might interfere with drug absorption • Secondary obesity as part of syndrome (e.g. Prader-Willi syndrome) • Weight reduction medication within 3-mo prior to visit 1A and until visit 2 • Impaired renal function • Indication of liver disease • History of needle phobia
General details about study	Two-week run in after screening then random assignment (1:1:1) to oral linagliptin, oral empagliflozin or placebo, stratified by age (<15 years, 15-<18) and gender to ensure ≤70% participants less than 15-years old and 30-70% participants were female. Due to dynamic nature of type 2 diabetes in young people, excluded participants on initial screening of modifiable criteria (e.g. HbA1c level) were allowed to re-screen up to 5 times. Double-blinded and double-dummy medication kits used for 26 weeks, then double-blind active treatment safety extension period to 52 weeks. Only short-term data at 26 weeks extracted.
Intervention(s)	**DPP-4 inhibitor** Oral linagliptin 5 mg/day for 52 weeks (first 26 weeks compared to placebo) **SGLT2 inhibitor** Empagliflozin 10/25 mg/day for 52 weeks (first 26 weeks compared to placebo) Initial randomisation to Empagliflozin 10 mg per day group. Empagliflozin pooled combined following groups • Empagliflozin 10 mg/day responders at week 12 (HbA1c<7%) and continued on 10 mg/day • Empagliflozin 10 mg/day non-responders at week 12 (HbA1c≥7%) and randomised at week 14 to 10 mg/day • Empagliflozin 10 mg/day non-responders at week 12 and randomised at week 14 to 25 mg/day • Empagliflozin 10 mg/day and no re-randomisation at week 14.

Comparator	Placebo for 26 weeks then re-randomsied to oral linagliptin 5 mg or to oral empagliflozin (10 mg or 25 mg) for 26 weeks.
Other publications associated with this study included in review	None reported
Secondary publication of another included study- see primary study for details	No
Sources of funding	The Boehringer Ingelheim; Eli Lilly and Company Alliance

Study arms

Empagliflozin (N = 52)
Oral empagliflozin 10/25 mg tablets for 52 weeks (first 26 weeks compared to placebo). Empagliflozin 10 mg/day (14 weeks) then if HbA1c >=7% at week 12 then re-randomised at week 14 to 10 mg/day or 25 mg/day (38 weeks) ; if HbA1c<7% at week 12 then stay on 10 mg/day (40 weeks)

Linagliptin (N = 53)
Oral linagliptin tablets 5 mg/day for 52 weeks (first 26 weeks compared to placebo)

Placebo then Empagliflozin or Linagliptin (N = 53)
Placebo (26 weeks) then re-randomised to oral empagliflozin 10 mg/day or 25 mg/day or oral linagliptin 5 mg/day (26 weeks)

Characteristics

Study-level characteristics

Characteristic	**Study (N = 157)**
% Female Sample size	n = 97 ; % = 62
Mean age (SD) Mean (SD)	14.53 (1.85)
All Other Sample size	n = 10 ; % = 6.4
American Indian or Alaska Native Sample size	n = 8 ; % = 6

Characteristic	Study (N = 157)
Asian Sample size	n = 9 ; % = 6
Black or African American Sample size	n = 49 ; % = 31
Native Hawaiian or other Pacific Islander Sample size	n = 3 ; % = 2
White Sample size	n = 78 ; % = 50
Non-Hispanic or non-Latino Sample size	n = 97 ; % = 62
Hispanic or Latino Sample size	n = 60 ; % = 38
<1 year Sample size	n = 51 ; % = 32.5
1 to 3 years Sample size	n = 66 ; % = 42
<3 years Sample size	n = 40 ; % = 25.5
Glycated haemoglobin (HbA1c) (%) Mean (SD)	8.03 (1.2)
Fasting Plasma Glucose (FPG) (mg/dL) Mean (SD)	158.6 (55.6)
Diet and exercise only due to metformin intolerance Sample size	n = 9 ; % = 5.7
Metformin only Sample size	n = 80 ; % = 51
Metformin and insulin Sample size	n = 63 ; % = 40.1
Insulin use at baseline	n = 68 ; % = 43.3

Characteristic	Study (N = 157)
Sample size	
Insulin only Sample size	n = 5 ; % = 3.2
Metformin and insulin Sample size	n = 63 ; % = 40.1

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Although little information about randomisation provided, likely randomised. Randomisation schedule generated and kept locked and secure from trial investigators.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Double-blind trial with double-dummy medication kits used.)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low *(Double-blinded, double-dummy medication kit used, ~10% non-adherance balanced across groups.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Missing data balanced across groups, ~10%. Sensitivity analysis for main HbA1c outcome did not detect difference in results.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(All outcomes appropriately assessed and objective except for patient-reported gastrointestinal symptoms)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Trial NCT03429543 and all changes to protocol, including intended outcomes, registered at clinicaltrials.gov)*
Overall bias and Directness	Risk of bias judgement	Low *(Low risk of bias for all domains)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable *(All participants children and young people with type 2 diabetes; ~91% participants on metformin (with or without insulin).)*

Shankar 2022

Bibliographic Reference	Shankar, R Ravi; Zeitler, Philip; Deeb, Asma; Jalaludin, Muhammad Yazid; Garcia, Raymundo; Newfield, Ron S; Samoilova, Yulia; Rosario, Carmen A; Shehadeh, Naim; Saha, Chandan K; Zhang, Yilong; Zilli, Martina; Scherer, Lynn W; Lam, Raymond L H; Golm, Gregory T; Engel, Samuel S; Kaufman, Keith D; A randomized clinical trial of the efficacy and safety of sitagliptin as initial oral therapy in youth with type 2 diabetes.; Pediatric diabetes; 2022; vol. 23 (no. 2); 173-182

Study details

Study type	Phase 3 Randomised controlled trial (RCT)
Blinding	Double blind
Trial registration number and/or trial name	NCT01485614
Number of participants	N=200
Duration of trial	54 weeks (20 weeks rescue period, 34 weeks rescue/treat to goal period)
Study setting	Various
Study location	Multisite (213 centres in 42 countries)
Study dates	02/2012 to 10/2019
Inclusion criteria	• Aged 10–17 years-old with Type 2 Diabetes diagnosis • HbA1c ≥6.5% - ≤10.0% if not on antihyperglycemic therapy, or ≥7.0% and ≤10.0% if on insulin therapy • BMI) ≥85th percentile or history of being overweight/obese at T2D diagnosis • Fasting C-peptide >0.6 ng/mL and FPG<13.3 mmol/L at randomisation
Exclusion criteria	• History of Type 1 Diabetes • Presence of anti-GAD or ICA-512 antibodies • Disorders other than Type 2 Diabetes known to affect glucose tolerance
General details about study	Originally a 16-week 4-arm trial (sitagliptin, metformin, placebo then metformin, placebo then sitagliptin) but amended to 2-arm only after beginning due to regulatory advice and protocol amendments. Two-step rescue plan involving blinded step (Step 1) and open-label step (Step 2) across two parts of trial (Part 1, weeks 0-20; Part 2, weeks 20-54). Until week 20 (Part 1), participants permitted rescue medication in form of blinded metformin if they exceeded progressively stricter glycaemic (fasting plasma glucose) thresholds; for participants not rescued during this period, rescue therapy from weeks 20-54 was blinded metformin (Sitagliptin group) or blinded sitagliptin (placebo then metformin group). Open-label rescue medication (Step 2)

	permitted for participants who continued to meet rescue criteria after Step 1 consisted of insulin or up-titration of pre-existing insulin therapy. From weeks 20-54 (Part 2), participants with HbA1c ≥7.0% could be treated to achieve HbA1c of <7.0% using blinded metformin or open-label insulin as appropriate (sitagliptin group), or blinded sitagliptin or open-label insulin as appropriate. During participant-blind placebo run-in period for both trials, and reinforced throughout trial duration, parents/guardians educated in pathophysiology and treatment of Type 2 Diabetes using materials adapted for use with young people with Type 2 Diabetes from the Lifestyle Intervention arm of the TODAY study (including nutritional advice and exercise recommendations). Reports baseline characteristics similar between groups but less females (57% vs 64%) and 10 to <15 year-olds (35% vs 50%) and more black participants (8% vs 2%) in sitagliptin group compared to placebo group.
Intervention(s)	Oral Sitagliptin 100 mg tablet prior to morning meal and 2 tablets of matching placebo to Metformin 500 mg prior to both morning and evening meal for 54 weeks.
Comparator	Matching placebo to Sitagliptin 100 mg tablet, once prior to morning meal, and 2 tablets of matching placebo to Metformin 500 mg prior to morning and evening meals. At weeks 20-54, matching placebo to Sitagliptin 100 mg tablet and 2 tablets of Metformin 500 mg prior to both morning and evening meals.
Other publications associated with this study included in review	None
Secondary publication of another included study- see primary study for details	No
Sources of funding	Funding provided by Merck Sharp & Dohme Corp., subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA
Outcome measures	• Glycated haemoglobin (HbA1c) level • Glucose level • Serious adverse events • Severe hypoglycaemic episode • Other gastrointestinal symptoms

Study arms

Sitagliptin (N = 96)

Oral sitagliptin 100 mg per day

Placebo then Metformin (N = 95)

Matching placebo (20 weeks) then oral metformin 1000 mg per day (34 weeks)

Characteristics

Study-level characteristics

Characteristic	Study (N = 190)
% Female	n = 115 ; % = 61

Characteristic	Study (N = 190)
Sample size	
Mean age (SD) (years) Mean (SD)	14 (2)
BMI (kg/m2) Mean (SD)	32.3 (7.8)
American Indian or Alaska Native Sample size	n = 15 ; % = 7.9
Asian Sample size	n = 29 ; % = 15.3
Black or African American Sample size	n = 10 ; % = 5.3
Hispanic or Latino Sample size	n = 71 ; % = 37.4
White Sample size	n = 98 ; % = 51.6
Duration of Type 2 Diabetes (years) Mean (SD)	0.7 (1.3)
Glycated haemoglobin (HbA1c) (%) Mean (SD)	7.5 (1.1)
Fasting Plasma Glucose (FPG) (mmol/L) Mean (SD)	7.7 (2.5)
Insulin use at baseline (Number of participants, %) Sample size	n = 22 ; % = 11.6

Critical appraisal

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High (No info about randomisation and differences in baseline characteristics (sex, age, ethnicity/race.)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low (Double-blind trial with ITT analysis.)

Cochrane Risk of Bias Tool 2.0		
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low (High rate of adherence to interventions.)
Domain 3: Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns (High proportion of missing data for long-term outcomes (40% vs 31% received rescue therapy weeks 0-54.)
Domain 4: Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low (Majority of outcomes laboratory based but some concerns for participant-reported outcomes.)
Domain 5 Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low (Results reported in line with trial protocol.)
Overall bias	Risk of bias judgement	High (High risk of bias regarding randomisation process (differences between groups at baseline, no information about randomisation) and some concerns about missing data.)
Directness	Overall Directness	Directly applicable (All participants 10-17 years-old with Type 2 Diabetes)

Tamborlane 2019

Bibliographic Reference	Tamborlane, William V; Barrientos-Perez, Margarita; Fainberg, Udi; Frimer-Larsen, Helle; Hafez, Mona; Hale, Paula M; Jalaludin, Muhammad Y; Kovarenko, Margarita; Libman, Ingrid; Lynch, Jane L; Rao, Paturi; Shehadeh, Naim; Turan, Serap; Weghuber, Daniel; Barrett, Timothy; Ellipse Trial, Investigators; Liraglutide in Children and Adolescents with Type 2 Diabetes.; The New England journal of medicine; 2019; vol. 381 (no. 7); 637-646

Study details

Study type	Phase 3 Randomised controlled trial (RCT)
Blinding	Double blind
Trial registration number and/or trial name	NCT01541215/ELLIPSE trial
Number of participants	N=135
Duration of trial	52 weeks (26 weeks double blind, 26 weeks open-label extension period)
Study setting	Various
Study location	Multisite (84 sites from 25 countries involved in screening)
Study dates	11/2012 to 05/2018
Inclusion criteria	• People with type 2 diabetes between 10-17 yrs-old • HbA1c 7-11% if treated with diet and exercise only or HbA1c 6.5-11% if treated with metformin with or without insulin • BMI>85th percentile (age- and sex- matched population as reference)
Exclusion criteria	• People with type 1 diabetes or maturity-onset diabetes of the young • Fasting C-peptide level<0.6 ng/ml • Use of any antidiabetic agent other than metformin and/or basal insulin within 90 days prior to screening • History of pancreatitis • Serum calcitonin levels of ≥50 ng/l • Personal or family history of medullary thyroid cancer or multiple endocrine neoplasia 2 • Alanine aminotransferase level 2.5 times upper limit of normal range or higher • Serum creatinine levels greater than upper limit of the normal range for age • Recent history of heart disease, proliferative retinopathy or maculopathy • Recurrent severe hypoglycemia or hypoglycemic unawareness
General details about study	Eleven to 12-wk run-in period on metformin, increased to maximum tolerated dose 1000-2000 mg/day, followed by 8 weeks maintenance. Eligibility criteria FPG 126-220 mg/dL and stable metformin dose. Participants on >2000 mg/day metformin continued on dose during trial. People on insulin reduced dose 20% at randomisation but dose could be increased to baseline dose after liraglutide dose escalation period. After 26 weeks, further 26-week open-label extension period with participants in liraglutide group continuing assignment and participants in placebo

	group remaining on metformin/insulin only. Diet and exercise counselling provided at several visits. No significant differences between groups in baseline characteristics.
Intervention(s)	Subcutaneous liraglutide at 0.6 mg/day, escalated in ~0.6 mg/week increments over course of 2-3 wks, then maintenance period to maximum of 1.8 mg/day. Dose adjustment based on side effects and efficacy of low dose.
Comparator	Placebo in visually identical prefilled pen injector, with same procedure as intervention.
Other publications associated with this study included in review	None
Secondary publication of another included study- see primary study for details	No
Sources of funding	Novo Nordisk; U.K. entities (inc. U.K. Medical Research Council, National Institutes of Health Research (NIHR) Translational Research Collaboration for Rare Diseases, and the NIHR Wellcome Clinical Research Facility) provided institutional grants to trial sites but no financial support to patients
Outcome measures	• Glycated haemoglobin (HbA1c) level • Glucose level • BMI z-score • Participants needing rescue medication in form of insulin • Serious adverse events • Severe hypoglycaemic episode • Other gastrointestinal symptoms

Study arms

Liraglutide (N = 66)

Subcutaneous liraglutide injection ≤1.8 mg per day

Placebo (N = 69)

Matching placebo

Characteristics

Study-level characteristics

Characteristic	Study (N = 134)
% Female Sample size	n = 83 ; % = 61.9
Mean age (SD) (years) Mean (SD)	14.6 (1.7)
BMI (z score) Mean (SD)	2.9 (1.3)
American Indian or Alaska Native	n = 3 ; % = 2.2

Characteristic	Study (N = 134)
Sample size	
Asian Sample size	n = 18 ; % = 13.4
Black Sample size	n = 16 ; % = 11.9
Hispanic or Latino ethnic group Sample size	n = 39 ; % = 29.1
Other Sample size	n = 10 ; % = 7.5
White Sample size	n = 87 ; % = 64.9
Duration of Type 2 Diabetes (years) Mean (SD)	1.9 (1.5)
Glycated haemoglobin (HbA1c) (%) Mean (SD)	7.8 (1.3)
Fasting Plasma Glucose (FPG) (mmol/L) Mean (SD)	8.4 (2.5)
Systolic blood pressure mmHg Mean (SD)	116.8 (11.8)
Diastolic blood pressure mmHg Mean (SD)	72.2 (8.1)
Metformin use/dose at baseline (mg/day) Mean (SD)	1894 (339)
Insulin use at baseline (Number of participants using insulin at baseline) Sample size	n = 25 ; % = 18.7

Critical appraisal

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low (Stratified randomisation using voice-response or web-based response system)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low (26-week double-blind trial with ITT analysis.)

Cochrane Risk of Bias Tool 2.0		
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low (Double-blind trial for 26 weeks with similar numbers in both groups completing treatment. Note open-label extension period for long-term (>26 weeks) data raises some concerns.)
Domain 3: Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low (ITT analysis with multiple imputation for missing data)
Domain 4: Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low (Note that long-term outcomes inc. adverse events are participant-reported and include open-label assessment period (>26 weeks) and so likely at high risk of bias.)
Domain 5 Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Results reported in accordance with trial protocol.)*
Overall bias	Risk of bias judgement	Low *(*Low risk of bias for short-term outcomes but some concerns regarding participant reported outcomes during open-label extension period.)

Cochrane Risk of Bias Tool 2.0		
Directness	Overall Directness	Directly applicable *(All participants were under-18 years, had type 2 diabetes and received metformin with or without basal insulin.)*

Tamborlane, Bishai 2022

Bibliographic Reference Tamborlane, William V; Bishai, Raafat; Geller, David; Shehadeh, Naim; Al-Abdulrazzaq, Dalia; Vazquez, Evelina Manica; Karoly, Eva; Troja, Tunde; Doehring, Orlando; Carter, Debra; Monyak, John; Sjostrom, C David; Once-Weekly Exenatide in Youth With Type 2 Diabetes.; Diabetes care; 2022; vol. 45 (no. 8); 1833-1840

Study details

Study type	Phase 3 Randomised controlled trial (RCT)
Blinding	Double blind
Trial registration number and/or trial name	NCT01554618
Number of participants	N=83
Duration of trial	24 weeks
Study setting	Various
Study location	Multisite (27 sites in 6 countries: Bulgaria, Hungary, Israel, Kuwait, Mexico, USA)
Study dates	05/2016 to 05/2020
Inclusion criteria	• People 10 to <18 yrs-old with Type 2 Diabetes • Glycated haemoglobin of 6.5-11% (48-97 mmol/mol) for participants not taking insulin or a sulfonylurea; 6.5-12% (48-108 mmol/mol) for participants taking insulin or a sulfonylurea.
Exclusion criteria	• C-peptide levels ≤0.6 ng/mL • Renal disease • Serum creatinine >1.5 mg/dL (132.6 mmol/L) in males or >1.4 mg/dL (123.8 mmol/L) in females
General details about study	Stratified randomisation (5:2 ratio) according to glycated haemoglobin at screening. Rescue medication (insulin) permitted for loss of glycaemic control and who required it remained in trial. At baseline, ~91% participants were taking metformin, 46% were taking insulin and 37.8% were taking metformin and insulin. One participant in exenatide group withdrew from study before receiving intervention and is not included in the ITT analysis. Reports baseline characteristics 'balanced' except that

	severe obesity more common in exenatide group (BMI [kg/m2] 36.86 [sd 9.28] in exenatide group vs 35.14 [sd 6.58] in placebo group).
Intervention(s)	Subcutaneous Exenatide 2 mg, once-weekly
Comparator	Matching placebo.
Secondary publication of another included study- see primary study for details	No
Sources of funding	AstraZeneca funded study and was involved in development of the design, data collection, analysis, and interpretation, writing article, and decision to submit for publication. Five co-authors were employees of AstraZeneca, two of which reported stocks from AstraZeneca. One co-author received honoraria for lectures and support from AstraZeneca for conducting the study. One co-author reported personal fees from PHASTAR and AstraZeneca during study. Main author reports grants from Yale University School of Medicine during study.
Outcome measures	• Glycated haemoglobin (HbA1c) level • Glucose level • Participants needing rescue medication in form of insulin • Serious adverse events • Severe hypoglycaemic episode • Other gastrointestinal symptoms

Study arms

Exenatide (N = 59)

Subcutaneous exenatide injection 2 mg per week

Placebo (N = 24)

Matching placebo

Characteristics

Study-level characteristics

Characteristic	Study (N = 82)
% Female Sample size	n = 48 ; % = 58.5
Mean age (SD) (years) Mean (SD)	15 (1.8)
BMI (kg/m2) Mean (SD)	36.4 (8.6)
American Indian or Alaska Native Sample size	n = 5 ; % = 6.1
Asian Sample size	n = 3 ; % = 3.7
Black or African American Sample size	n = 25 ; % = 30.5
Hispanic or Latino ethnic group	n = 33 ; % = 44

Characteristic	Study (N = 82)
Sample size	
Other Sample size	n = 14 ; % = 17.1
White Sample size	n = 35 ; % = 42.7
Duration of Type 2 Diabetes (years) Mean (SD)	2 (2)
Glycated haemoglobin (HbA1c) (%) Mean (SD)	8.2 (1.3)
Fasting Plasma Glucose (FPG) (mmol/L) Mean (SD)	9.3 (3.3)
Metformin use/dose at baseline Sample size	n = 65 ; % = 79.2
Metformin only Sample size	n = 33 ; % = 40.2
Metformin plus insulin Sample size	n = 31 ; % = 37.8
Metformin plus a sulfonylurea Sample size	n = 1 ; % = 1.2
Insulin use at baseline Sample size	n = 38 ; % = 46.3

Critical appraisal

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns (No info about randomisation method and reports more severe obesity in exenatide group)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low (Double-blind trial with ITT analysis.)
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low (High rate of adherence with ~95% using >80% of trial medication.)

Cochrane Risk of Bias Tool 2.0		
Domain 3: Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns (~15% percentage of missing data in exenatide group and no sensitivity analysis reported.)
Domain 4: Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low (Main outcomes are laboratory assessed, but some concerns for participant-reported outcomes.)
Domain 5 Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low (Reports primary and second efficacy endpoints, and adverse events, as stated in trial protocol.)
Overall bias	Risk of bias judgement	Moderate (Some concerns regarding risk of bias from randomisation process and missing data.)
Directness	Overall Directness	Directly applicable (All participants under-18 years and had type 2 diabetes; 91.5% of participants were receiving metformin with or without insulin or a sulfonylurea.)

Tamborlane, Laffel 2022

Bibliographic Reference Tamborlane, William V; Laffel, Lori M; Shehadeh, Naim; Isganaitis, Elvira; Van Name, Michelle; Ratnayake, Jayantha; Karlsson,

Cecilia; Norjavaara, Ensio; Efficacy and safety of dapagliflozin in children and young adults with type 2 diabetes: a prospective, multicentre, randomised, parallel group, phase 3 study.; The lancet. Diabetes & endocrinology; 2022; vol. 10 (no. 5); 341-350

Study details

Study type	Phase 3 Randomised controlled trial (RCT)
Blinding	Double blind
Trial registration number and/or trial name	NCT02725593
Number of participants	N=72
Duration of trial	24-weeks
Study setting	Various
Study location	Multisite (30 centres in 5 countries: Hungary, Israel, Mexico, Russia, USA)
Study dates	06/2016 to 03/2019
Inclusion criteria	• Aged 10-24 years-old with Type 2 Diabetes • HbA1c concentration of 6·5–11% (48–97 mmol/mol) • Fasting plasma glucose ≤14·2 mmol/L (≤255 mg/dL) • Stable dose of either metformin (≥1000 mg daily), insulin, or a combination of metformin (≥1000 mg daily) and insulin for a minimum of 8 weeks
Exclusion criteria	• Previous Type 1 Diabetes diagnosis • Monogenic cause of type 2 diabetes • Genetic disorders with strong associations with insulin resistance
General details about study	Web and voice-response system for stratified randomisation according to sex, age and background medication (metformin, insulin, or metformin and insulin). Four-week lead-in period. Rescue medication in form of basal insulin permitted for lack of glycaemic control. Participants needing rescue medication continued in trial. Twenty-six per cent of participants were aged 18-24 years. Reports baseline differences in 5 characteristics: more European (41% in dapagliflozin group vs 24% in placebo group), more White participants (72% vs 46%), lower FPG concentration (8.66 [sd 3.09] mmol/L vs 9.27 [sd 3.51]), lower BMI (31.3 [7.5] kg/m2 vs 33.6 [sd 8.8]) and more use of insulin (56% vs 39%).
Intervention(s)	Oral dapagliflozin 10 mg, once daily, for 24 weeks, in addition to standard care (metformin and/or insulin).
Comparator	Placebo, in addition to standard care.
Other publications associated with this study included in review	None
Secondary publication of	No

another included study- see primary study for details	
Sources of funding	Funded by AstraZeneca
Outcome measures	• Glycated haemoglobin (HbA1c) level • Glucose level • BMI z-score • Participants needing rescue medication in form of insulin • Serious adverse events • Diabetic Ketoacidosis (DKA) or Hyperosmolar Hyperglycaemic State (HHS) • Severe hypoglycaemic episode • Other gastrointestinal symptoms

Study arms

Dapagliflozin (N = 39)

Oral dapagliflozin 10 mg per week

Placebo (N = 33)

Matching placebo

Characteristics

Study-level characteristics

Characteristic	Study (N = 72)
% Female Sample size	n = 43 ; % = 59.7
Mean age (SD) (years) Mean (SD)	16.2 (3.4)
BMI Mean (SD)	32.4 (8.1)
Black or African American Sample size	n = 18 ; % = 25
Native American or Alaska Native Sample size	n = 5 ; % = 6.9
Other Sample size	n = 5 ; % = 6.9
White Sample size	n = 44 ; % = 61.1
Duration of Type 2 Diabetes (years) Mean (SD)	3.1 (2.8)
Glycated haemoglobin (HbA1c) (%) Mean (SD)	7.9 (1.4)
Fasting Plasma Glucose (FPG) (mmol/L) Mean (SD)	8.9 (3.3)
Systolic blood pressure mmHg	118.9 (13.9)

Characteristic	Study (N = 72)
Mean (SD)	
Diastolic blood pressure mmHg Mean (SD)	74.5 (8.3)
Metformin use/dose at baseline (Number of participants, %; mg/day) Sample size	n = 60 ; % = 84
Metformin use/dose at baseline (Number of participants, %; mg/day) Mean (SD)	1647 (494)
Metformin only Sample size	n = 37 ; % = 51
Metformin plus basal insulin Sample size	n = 23 ; % = 32
Insulin use at baseline (Number of participants, %) Sample size	n = 35 ; % = 49
Insulin only Sample size	n = 12 ; % = 17
Metformin plus basal insulin Sample size	n = 23 ; % = 32

Critical appraisal

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns (Interactive web and voice response system for randomisation and allocation concealment although there were imbalances in 5 baseline characteristics (ethnicity/race, FPG level, BMI, basal insulin use).
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low (Double-blind trial with ITT analysis)

Cochrane Risk of Bias Tool 2.0		
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low (Double-blind trial with number of participants deviating from protocol balanced across groups)
Domain 3: Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns (Only 82% and 76% of participants in dapagliflozin and placebo groups, respectively, were receiving treatment at end of double-blind period; sensitivity analysis using per-protocol population changed results.)
Domain 4: Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low (Main outcomes are laboratory assessed, but some concerns for participant-reported outcomes.)
Domain 5 Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low (Primary and secondary endpoints, as well as adverse events, reported in line with trial protocol.)
Overall bias	Risk of bias judgement	Moderate (Some concerns regarding randomisation process and missing data.)

Cochrane Risk of Bias Tool 2.0		
Directness	Overall Directness	

Wheeler 2018

Bibliographic Reference Wheeler, Mark D; Barrientos-Perez, Margarita; Lo, Fu-Sung; Liang, Bo; Lunsford, Alison; Thorisdottir, Olof; Zuckerman-Levin, Nehama; A 26-week, randomized trial of insulin detemir versus NPH insulin in children and adolescents with type 2 diabetes (iDEAt2).; European journal of pediatrics; 2018; vol. 177 (no. 10); 1497-1503

Study details

Study type	Phase 3 Randomised controlled trial (RCT)
Blinding	Open label
Trial registration number and/or trial name	NCT02131272/iDEAt2 trial
Number of participants	N=42
Duration of trial	26 weeks
Study setting	Various
Study location	Multisite (12 countries: Brazil, Hungary, Germany, India, Israel, South Korea, Malaysia, Mexico, Russia, Taiwan, Turkey, USA)
Study dates	06/2014 to 06/2016
Inclusion criteria	• Aged 10-17 years-old • Diagnosis of Type 2 Diabetes ≥3-mo prior to screening • HbA1c ≥7%-≤10.5% at screening • Insufficient glycaemic control with maximum tolerated dose of metformin with or without other oral antidiabetic drugs with or without basal insulin
Exclusion criteria	• Presence of known or suspected hypersensitivity to trial products • Maturity-onset diabetes of the young • Impaired liver function (alanine aminotransferase ≥ 2.5 times upper limit) • Known proliferative retinopathy or maculopathy requiring acute treatment • Pregnancy, breastfeeding, or willingness to become pregnant • Treatment with any medication other than metformin with or without other OADs with or without basal insulin for the indication of diabetes or obesity ≤3-mo prior to screening
General details about study	Two-week screening period then randomisation. Treatment with other oral antidiabetic drug discontinued during trial. All participants received metformin, diet and exercise interventions for 26 weeks. Insulin-naive participants initiated at 0.1-0.2 U/kg to maximum dose of 10U; participants already on basal insulin switched to equivalent unit of insulin detemir or NPH and pre-trial daily injection frequency, as appropriate. Note that trial was terminated early by sponsor due to problems recruiting sufficient participants (determined to be 358) to demonstrate non-inferiority

	of insulin detemir to NPH insulin. Differences between baseline characteristics of insulin detemir and NPH insulin groups include duration of diabetes (2.3 [sd 1.9) years vs 3.3 [1.7] years), ethnicity (95% vs 81% Black or Asian), HbA1c (8.7% [sd 0.9] vs 9% [sd 1.1]), and FPG (8 mmol/L [2.5] vs 10.2 mmol/L [3.5]).
Intervention(s)	Subcutaneous insulin detemir 100 U/mL, via 3 mL pre-filled FlexPen (Novo Nordisk), once or twice daily.
Comparator	Subcutaneous Neutral protamine Hagedorn (NPH) 100 IU/mL, via 3 mL pre-filled FlexPen (Novo Nordisk), once or twice daily.
Other publications associated with this study included in review	None
Secondary publication of another included study- see primary study for details	No
Sources of funding	Sponsored by NovoNordisk A/S. Medical writing and submission support provided by Watermeadow Medical—an Ashfield company, part of UDG Healthcare PLC, funded by Novo Nordisk A/S.
Outcome measures	• Glycated haemoglobin (HbA1c) level • Glucose level • BMI z-score • Participants needing rescue medication in form of insulin • Serious adverse events • Severe hypoglycaemic episode • Other gastrointestinal symptoms

Study arms

Insulin detemir (N = 20)

Subcutaneous insulin detemir injection 100 or 200 U/mL per day

Neutral protamine Hagedorn (NPH) insulin (N = 22)

Subcutaneous neutral protamine Hagedorn (NPH) insulin 100 or 200 IU/mL per day

Characteristics

Study-level characteristics

Characteristic	Study (N = 42)
% Female Sample size	n = 27 ; % = 64.2
10-14 years Sample size	n = 20 ; % = 47.6
15-17 years Sample size	n = 22 ; % = 52.4
BMI (kg/m2)	28.2 (5.8)

Characteristic	Study (N = 42)
Mean (SD)	
American Indian or Alaska Native Sample size	n = 1 ; % = 2.4
Asian Sample size	n = 18 ; % = 42.8
Black Sample size	n = 1 ; % = 2.4
Hispanic or Latino Sample size	n = 15 ; % = 35.7
Other Sample size	n = 3 ; % = 7.1
White Sample size	n = 19 ; % = 45.2
Duration of Type 2 Diabetes (years) Mean (SD)	2.8 (1.9)
Glycated haemoglobin (HbA1c) (%) Mean (SD)	8.8 (1)
Fasting Plasma Glucose (FPG) (mmol/L) Mean (SD)	9.2 (3.2)
Metformin use/dose at baseline (Number of participants, %) Sample size	n = 42 ; % = 100
Metformin only Sample size	n = 9 ; % = 21.4
Metformin plus basal insulin +/- oral antidiabetic drug Sample size	n = 33 ; % = 78.6
Insulin use at baseline Sample size	n = 33 ; % = 78.6

Critical appraisal

Cochrane Risk of Bias Tool 2.0		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High (No information about randomisation nor allocation concealment, insufficiently powered. Reports that there are baseline differences between groups but does not elaborate which may be significant.)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns (ITT analysis conducted but open-label trial.)
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low (93% adherence in trial but open-label.)
Domain 3: Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low (ITT analysis conducted for primary outcome but not for secondary/safety endpoints due to failure to recruit sufficient participants in trial.)

Cochrane Risk of Bias Tool 2.0		
Domain 4: Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low (Main outcomes are laboratory assessed, but some concerns for participant-reported outcomes.)
Domain 5 Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low (Results reported in line with trial protocol.)
Overall bias	Risk of bias judgement	High (High risk of bias regarding randomisation process and some concerns about lack of blinding/open-label nature of trial).
Directness	Overall Directness	Directly applicable (All participants 10-17 years-old with Type 2 Diabetes)

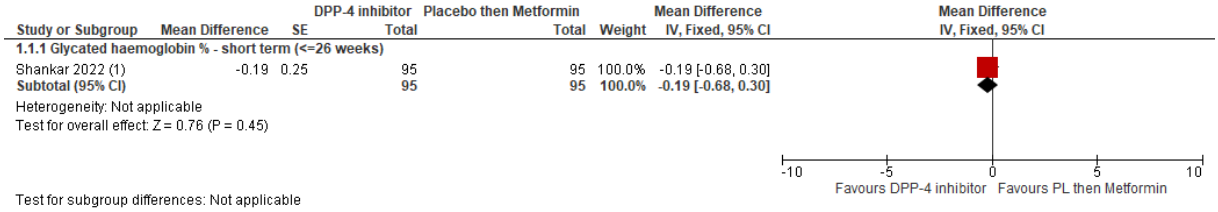
Appendix E – Forest plots

Unless otherwise stated, for continuous outcomes, a mean difference <0, or for relative risk outcomes, a risk ratio <1, indicates that the intervention (on the left-hand side of forest plot) is favoured over the control (on the right-hand side of forest plot).

Second-line treatment

DPP-4 inhibitor (Sitagliptin) vs Placebo then Metformin – Short- (≤26 weeks) and long-term (>26 weeks) outcomes

Glycated haemoglobin (HbA1c) % - short-term change score

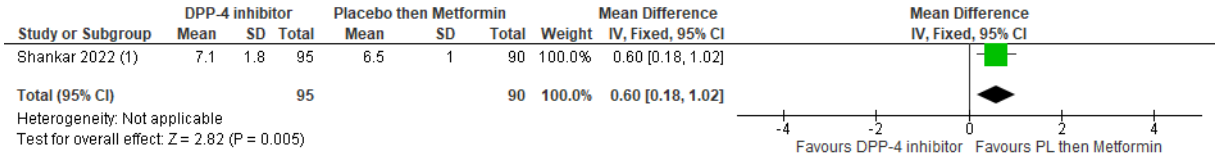


Test for subgroup differences: Not applicable

Footnotes

(1) Once daily sitagliptin 100 mg compared to placebo for 20 weeks.

Glycated haemoglobin (HbA1c) % - long-term post-intervention score

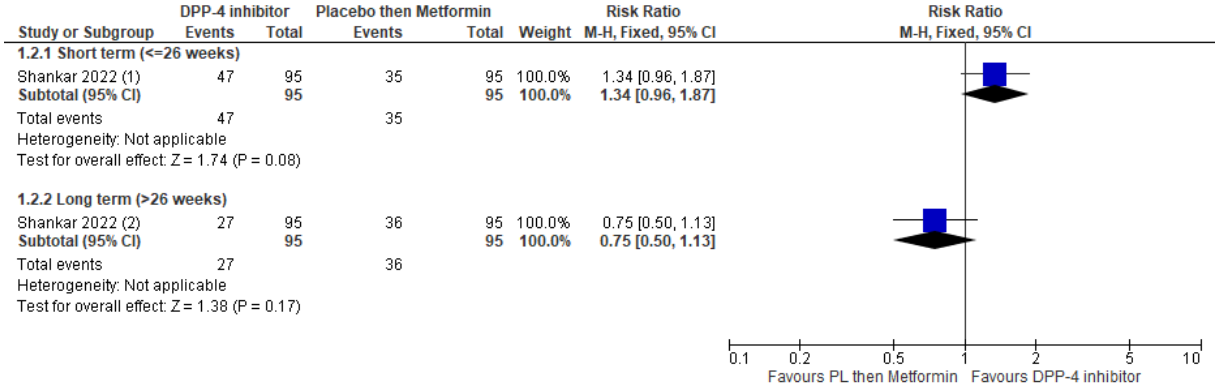


Footnotes

(1) As above for 20 weeks then twice daily metformin 1000 mg for 34 weeks.

Participants with glycated haemoglobin (HbA1c)≤<7%

(RR more than 1 favours DPP-4 inhibitor)

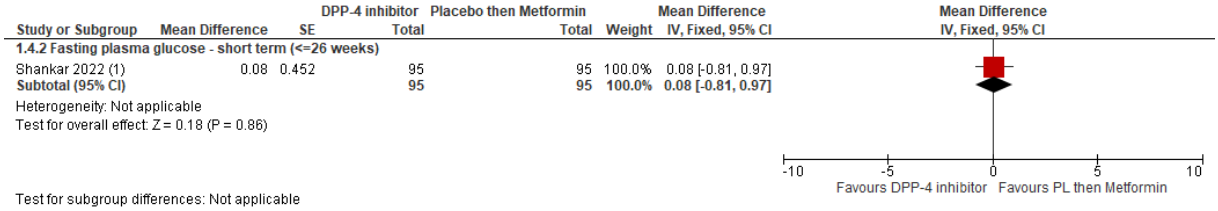


Footnotes

(1) Once daily sitagliptin 100 mg compared to placebo for 20 weeks.

(2) As above and then twice daily metformin 1000 mg for 34 weeks.

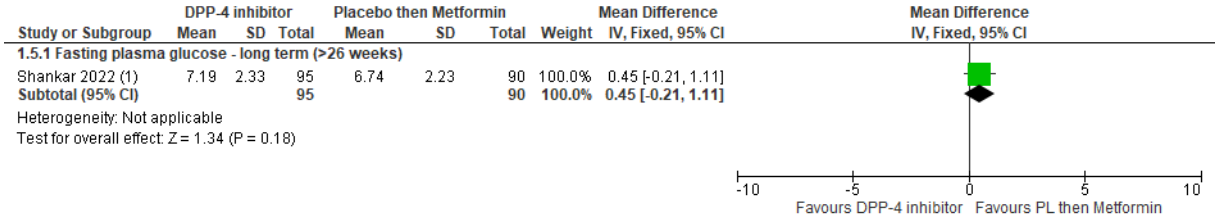
Fasting plasma glucose (mmol/L) – short-term change score



Footnotes

(1) Once daily sitagliptin 100 mg compared to placebo for 20 weeks.

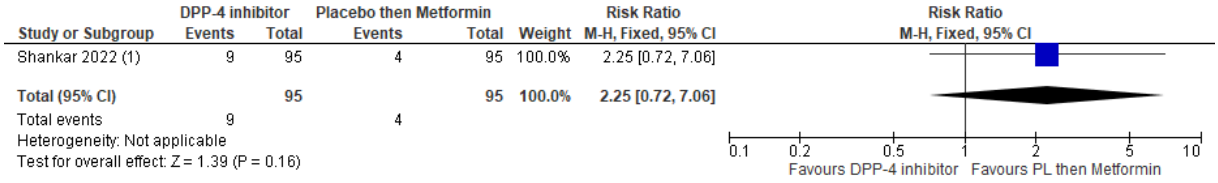
Fasting plasma glucose (mmol/L) – long-term change score



Footnotes

(1) As above and then twice daily metformin 1000 mg for 34 weeks.

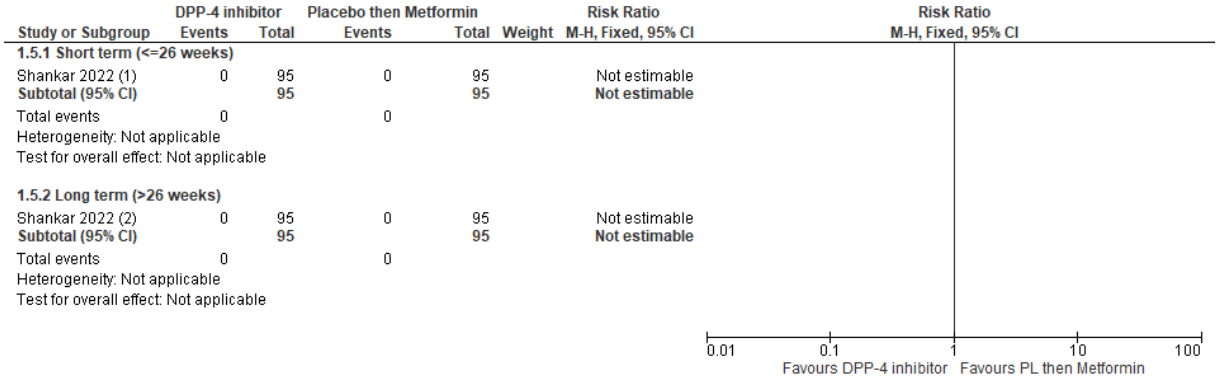
Serious adverse events – long term (>26 weeks)



Footnotes

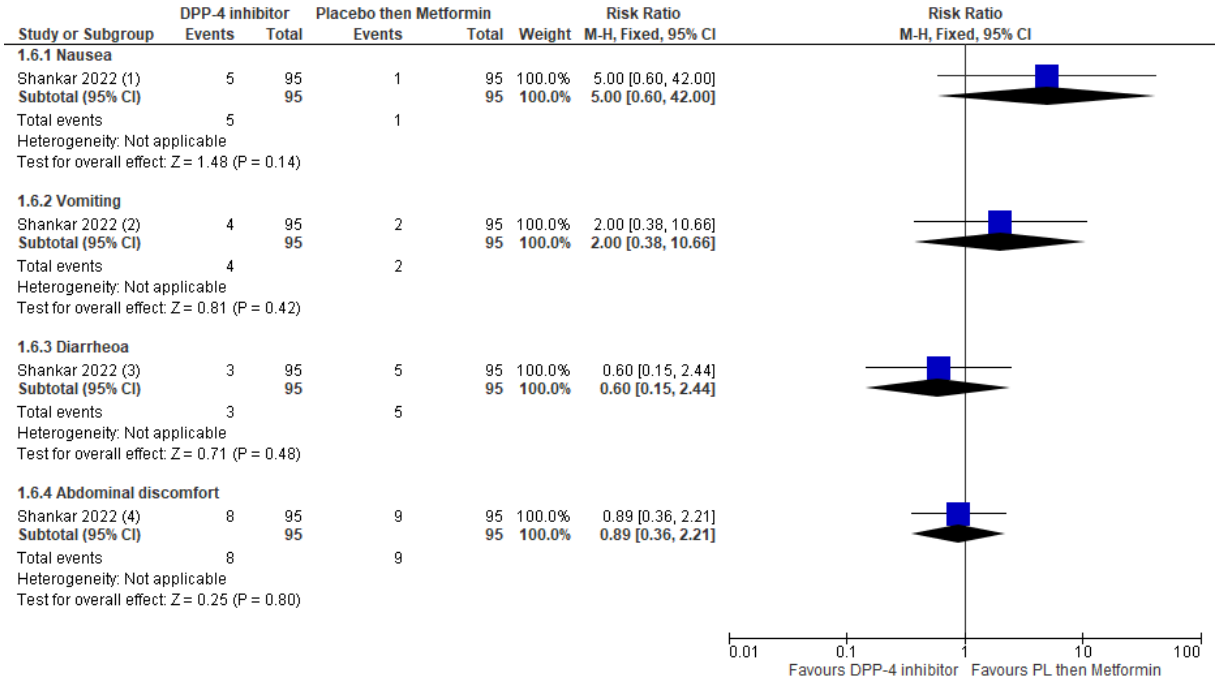
(1) 0-54 weeks. Once daily sitagliptin 100 mg compared to placebo for 20 weeks and then twice daily metformin 1000 mg for 34 weeks.

Severe hypoglycaemic episode



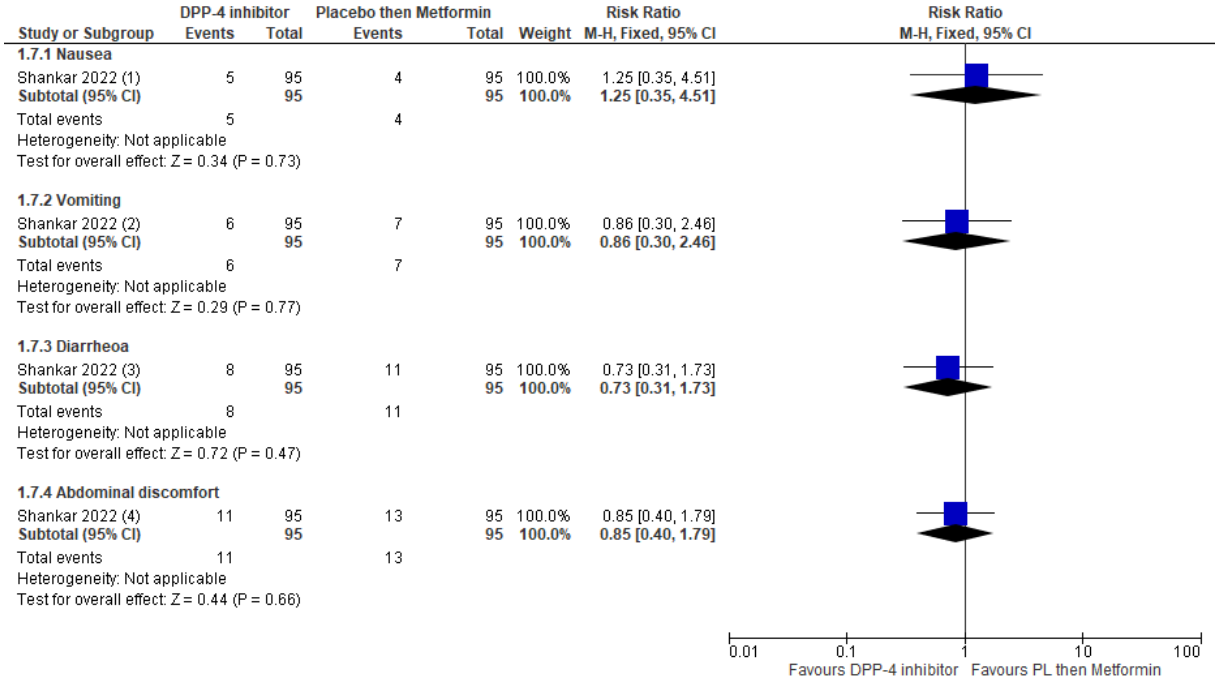
Footnotes
(1) 0-20 weeks. 'Severe'=symptomatic episode requiring medical/non-medical assistance. Once daily sitagliptin 100 mg compared to placebo for 20 weeks.
(2) 0-54 weeks. As above and then twice daily metformin 1000 mg for 34 weeks.

Other gastrointestinal symptoms – Short-term (≤26 weeks)



Footnotes
(1) 0-20 weeks. Once daily sitagliptin 100 mg compared to placebo.
(2) See note 1 above.
(3) See note 1 above.
(4) Includes lower abdominal pain, upper abdominal pain, abdominal pain, abdominal discomfort, and epigastric discomfort. See note 1 above.

Other gastrointestinal symptoms – Long-term (>26 weeks)



Footnotes

(1) 0-54 weeks. Once daily sitagliptin 100 mg compared to placebo for 20 weeks and then twice daily metformin 1000 mg for 34 weeks.

(2) See note 1 above.

(3) See note 1 above.

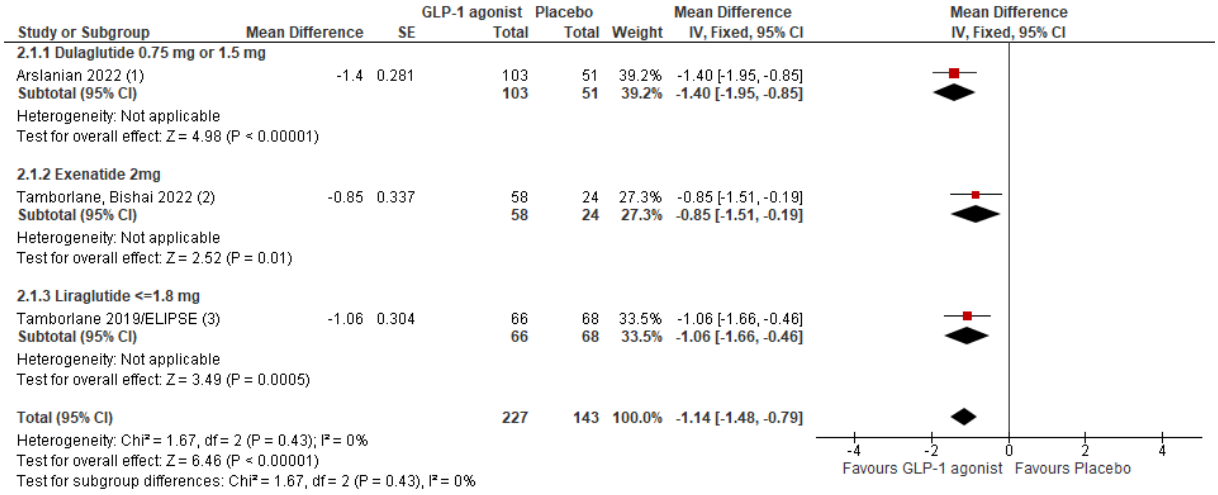
(4) Includes lower abdominal pain, upper abdominal pain, abdominal pain, abdominal discomfort, and epigastric discomfort. See note 1 above.

Metformin combination therapy

GLP-1 receptor agonist vs Placebo

Short-term outcomes (≤26 weeks)

Glycated haemoglobin (HbA1c) % - change score

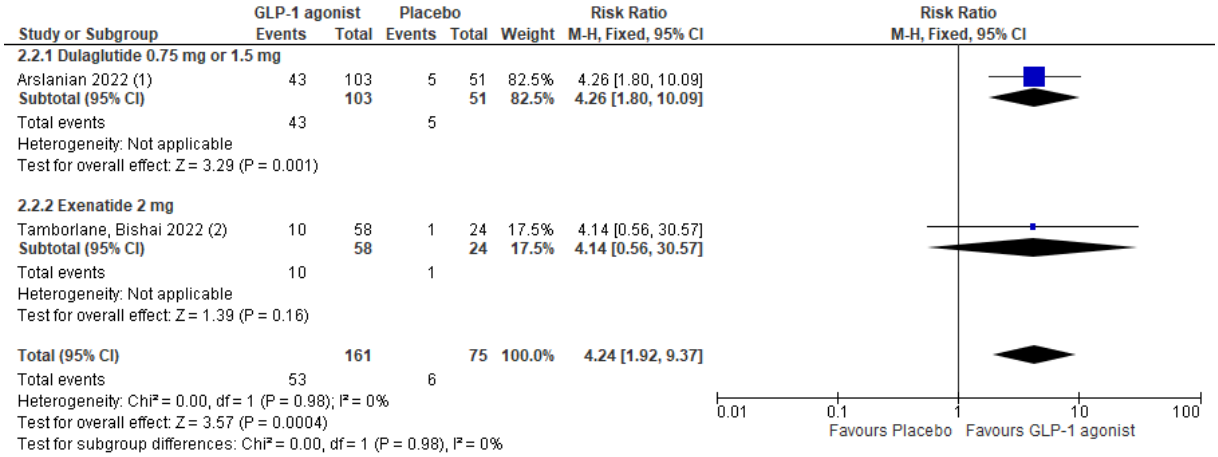


Footnotes

(1) Once weekly for 26 weeks. 78% of participants receiving metformin with or without insulin. Data from pooled analysis of dulaglutide 0.75 mg and 1.5 mg arms.
(2) Once weekly for 24 weeks. 91.5% of participants taking metformin with or without insulin or sulfonylurea.
(3) Maximum daily dose for 26 weeks.

Participants with glycated haemoglobin (HbA1c)≤6.5%

(RR more than 1 favours GLP-1 receptor agonist)

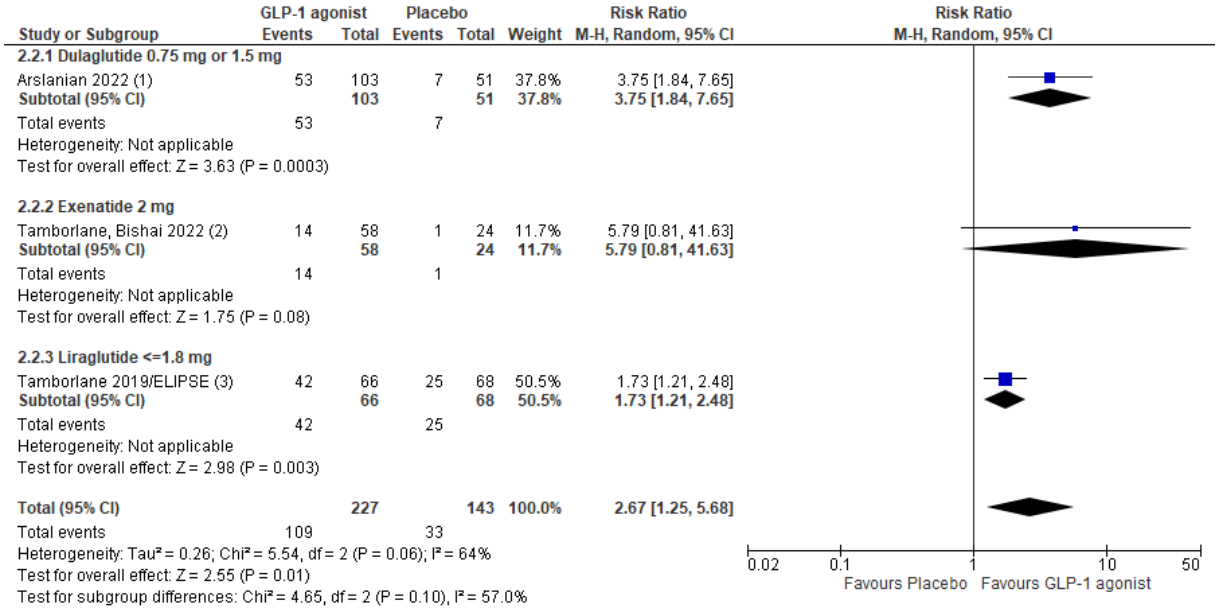


Footnotes

(1) Once weekly for 26 weeks. 78% of participants receiving metformin with or without insulin. Data from pooled analysis of dulaglutide 0.75 mg and 1.5 mg arms.
(2) Once weekly for 24 weeks. Data extrapolated from supplementary figure S3. 91.5% of participants taking metformin with or without insulin or sulfonylurea.

Participants with glycated haemoglobin (HbA1c)≤<7%

(RR more than 1 favours GLP-1 receptor agonist)

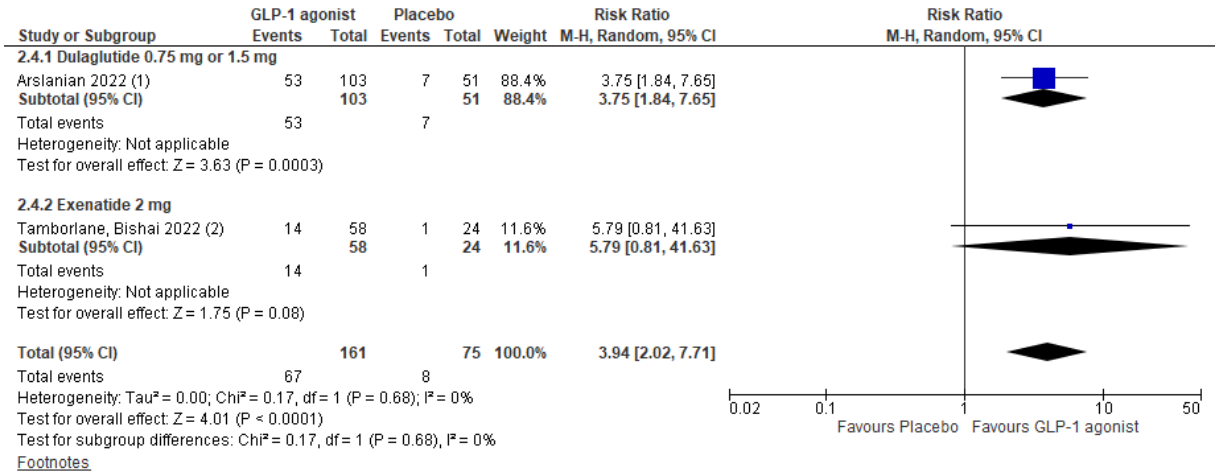


Footnotes

(1) Once weekly for 26 weeks. 78% of participants receiving metformin with or without insulin. Data from pooled analysis of dulaglutide 0.75 mg and 1.5 mg arms.
(2) Once weekly for 24 weeks. Data extrapolated from supplementary figure S3. 91.5% of participants taking metformin with or without insulin or sulfonylurea.
(3) Maximum daily dose for 26 weeks.

Subgroup analysis: Participants with HbA1c<7%

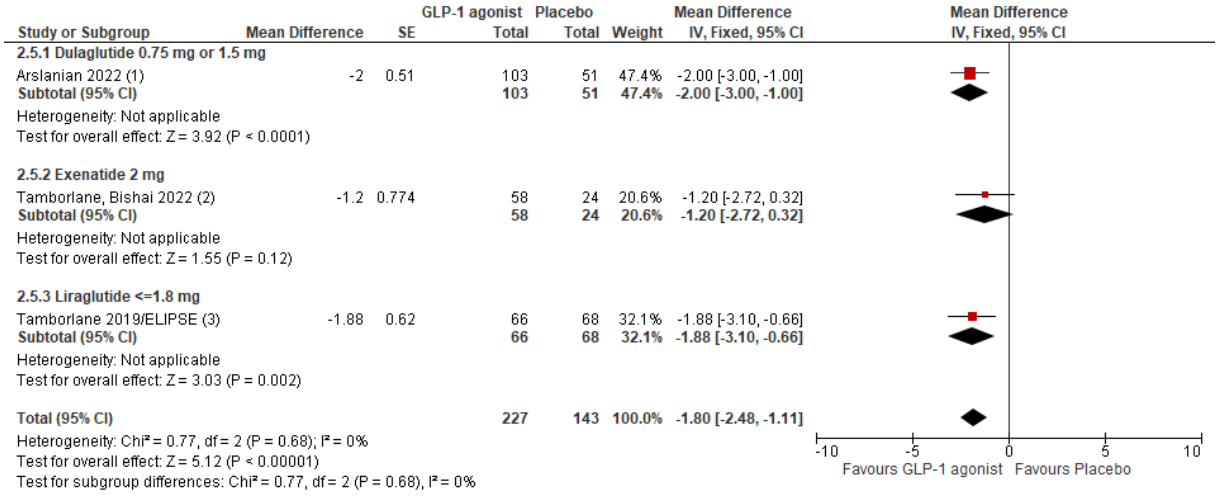
(RR more than 1 favours GLP-1 receptor agonist)



Footnotes

(1) Once weekly for 26 weeks. 78% of participants receiving metformin with or without insulin. Data from pooled analysis of dulaglutide 0.75 mg and 1.5 mg arms.
(2) Once weekly for 24 weeks. Data extrapolated from supplementary figure S3. 91.5% of participants taking metformin with or without insulin or sulfonylurea.

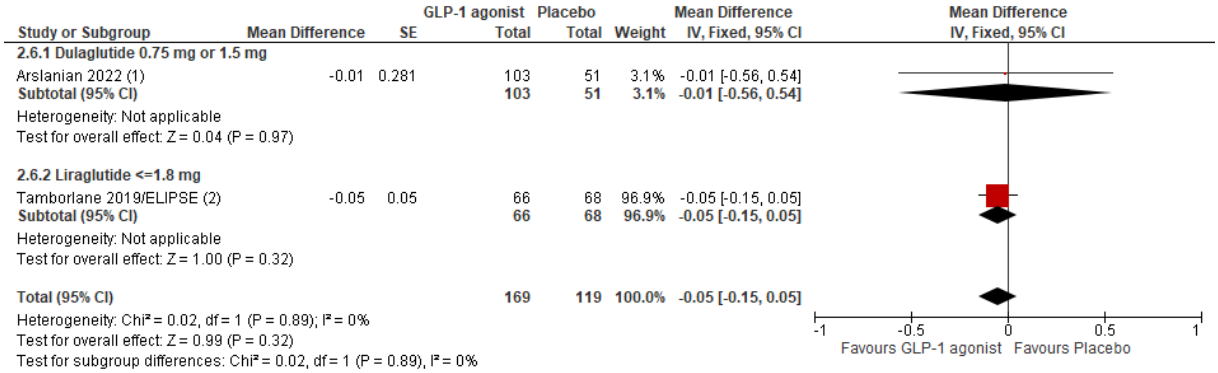
Fasting plasma glucose (mmol/L) – change score



Footnotes

(1) Once weekly for 26 weeks. 78% of participants receiving metformin with or without insulin. Data from pooled analysis of dulaglutide 0.75 mg and 1.5 mg arms.
(2) Once weekly for 24 weeks. 91.5% of participants taking metformin with or without insulin or sulfonylurea.
(3) Maximum daily dose for 26 weeks.

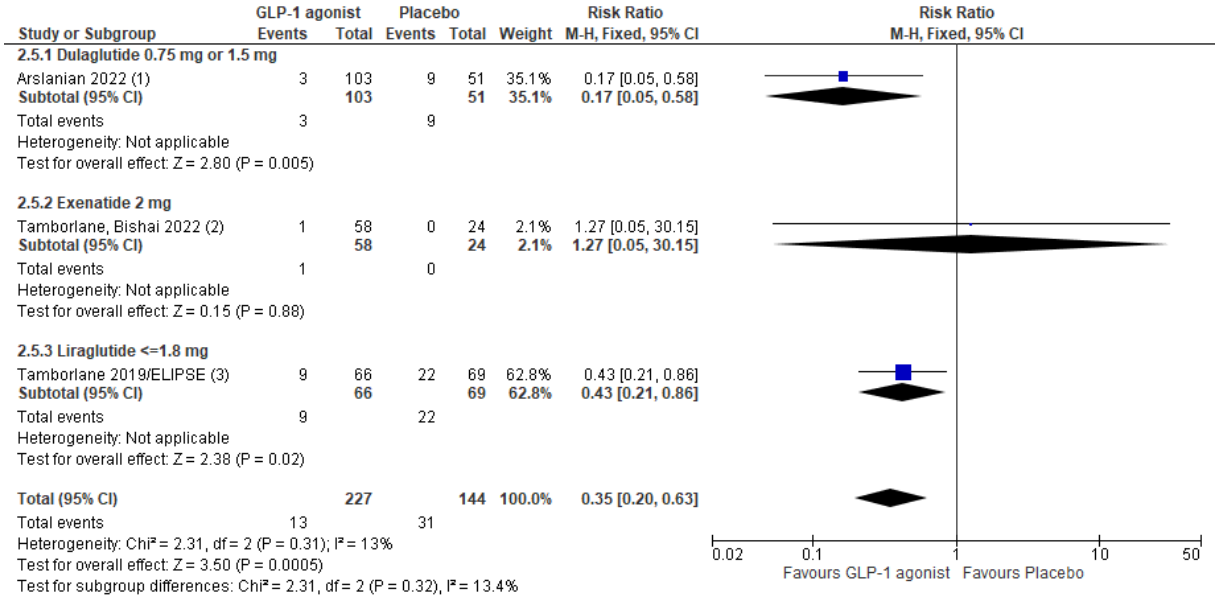
BMI z-score – change score



Footnotes

(1) Once weekly for 26 weeks. 78% of participants receiving metformin with or without insulin. Data from pooled analysis of dulaglutide 0.75 mg and 1.5 mg arms.
(2) Maximum daily dose for 26 weeks.

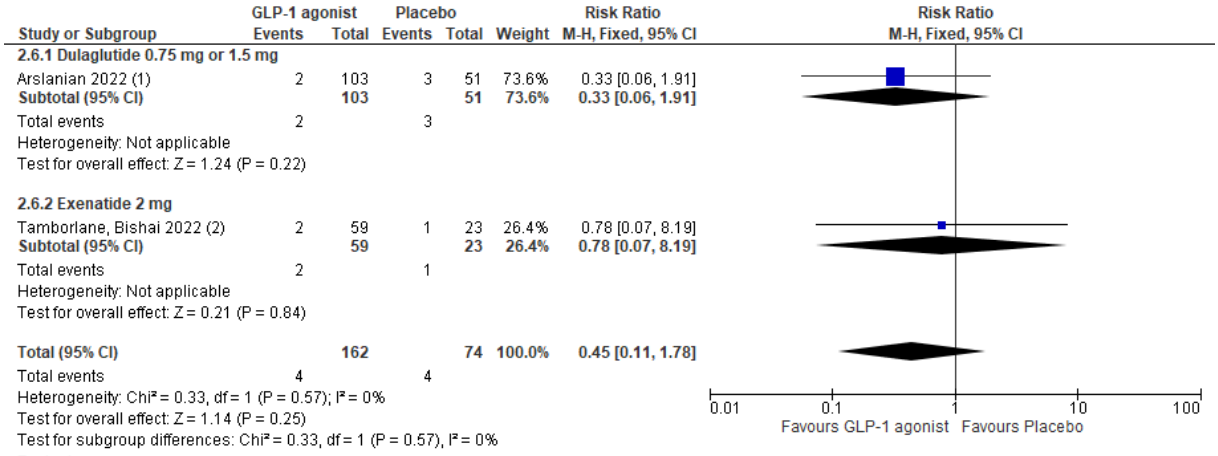
Participants needing rescue medication in form of insulin



Footnotes

(1) Once weekly for 26 weeks. 78% of participants receiving metformin with or without insulin. Data from pooled analysis of dulaglutide 0.75 mg and 1.5 mg arms.
(2) Once weekly for 24 weeks. 91.5% of participants taking metformin with or without insulin or sulfonylurea.
(3) Maximum daily dose for 26 weeks.

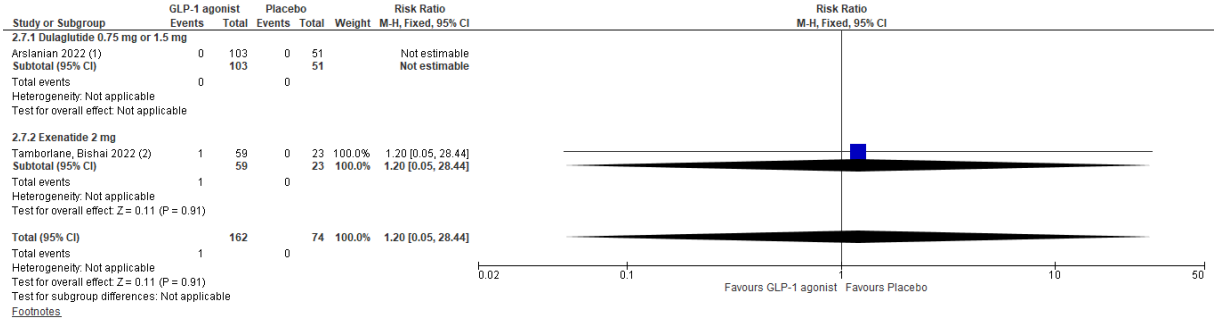
Serious adverse events



Footnotes

(1) Once weekly for 26 weeks. 78% of participants receiving metformin with or without insulin. Data from pooled analysis of dulaglutide 0.75 mg and 1.5 mg arms.
(2) Once weekly for 24 weeks. 91.5% of participants taking metformin with or without insulin or sulfonylurea.

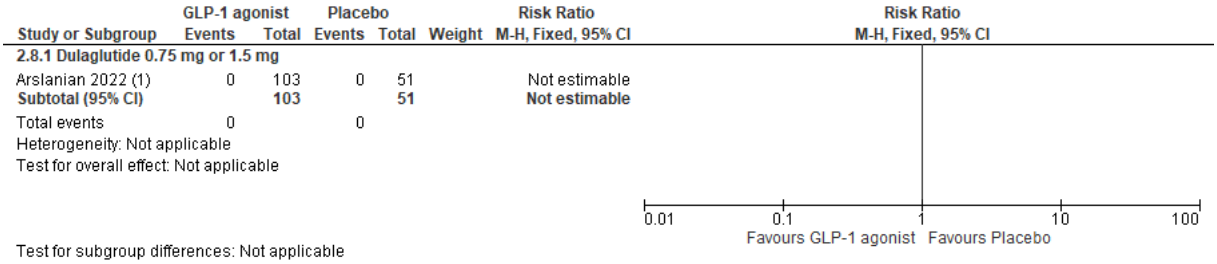
Severe hypoglycaemic episode



Footnotes

(1) Once weekly for 26 weeks. 'Severe' defined as episode requiring assistance of another person to actively treat. 78% of participants receiving metformin with or without insulin. Data from pooled analysis of dulaglutide 0.75 mg and 1.5 mg arms.
(2) Once weekly for 24 weeks. ADA Classification of 'severe'=an episode requiring assistance of another person. Study also reports no events in either arm for 'Major hypoglycaemia'.

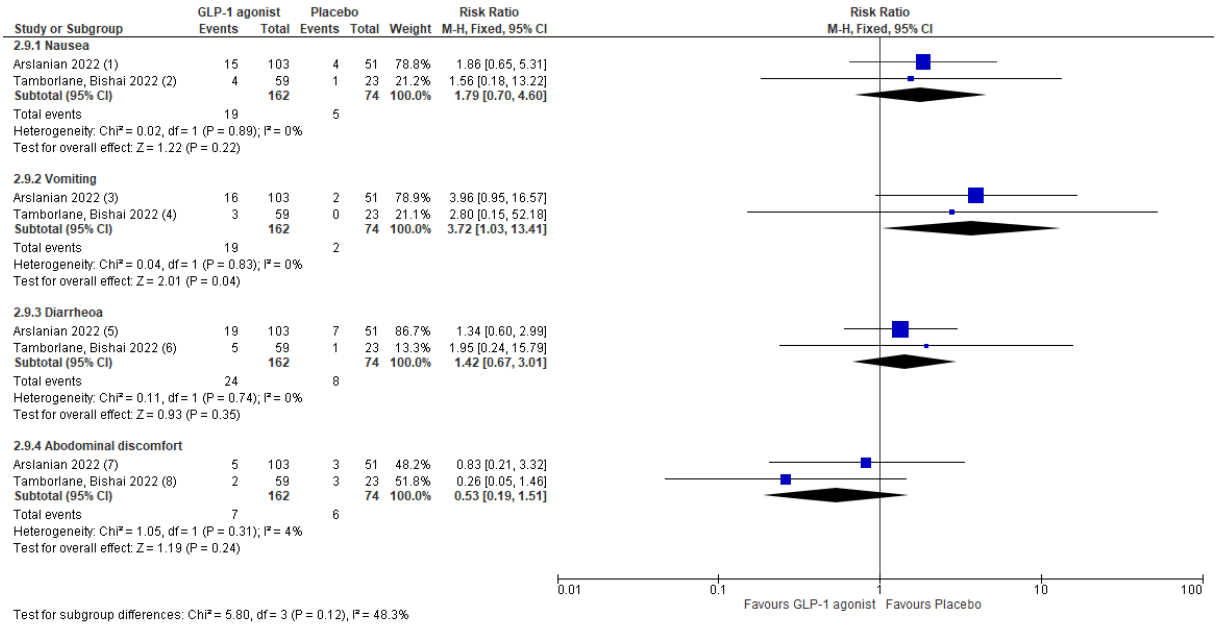
Pancreatitis



Footnotes

(1) Once weekly for 26 weeks. 78% of participants receiving metformin with or without insulin. Data from pooled analysis of dulaglutide 0.75 mg and 1.5 mg arms.

Other gastrointestinal symptoms

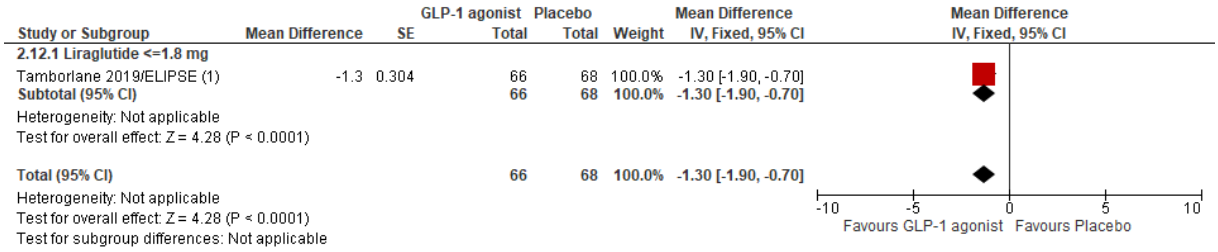


Footnotes

(1) 0-26 weeks. Once weekly dulaglutide 0.75 mg or 1.5 mg for 26 weeks. 78% of participants receiving metformin with or without insulin. Data from pooled analysis of dulaglutide 0.75 mg and 1.5 mg arms.
(2) 0-24 weeks. Once weekly exenatide 2mg for 24 weeks. 91.5% of participants taking metformin with or without insulin or sulfonylurea.
(3) See note 1 above.
(4) See note 2 above.
(5) See note 1 above.
(6) See note 2 above.
(7) Data reported includes abdominal pain, abdominal cramping, colic and intermittent right-side abdominal pain. See note 1 above.
(8) See note 2 above.

Long-term outcomes (>26 weeks)

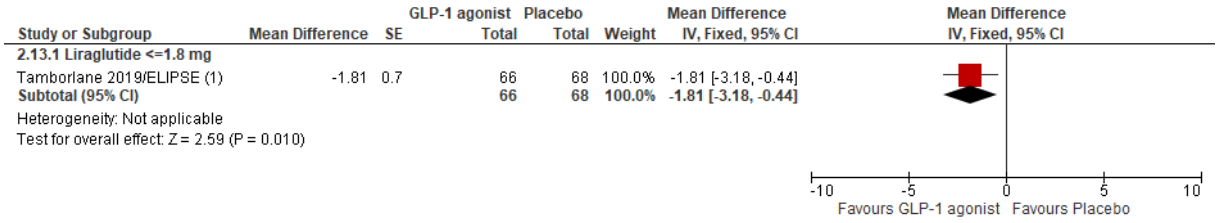
Glycated haemoglobin (HbA1c) % - change score



Footnotes

(1) Maximum daily dose. Participants from weeks 26 to 52 discontinued placebo but continued metformin (with or without insulin) from weeks 0-26.

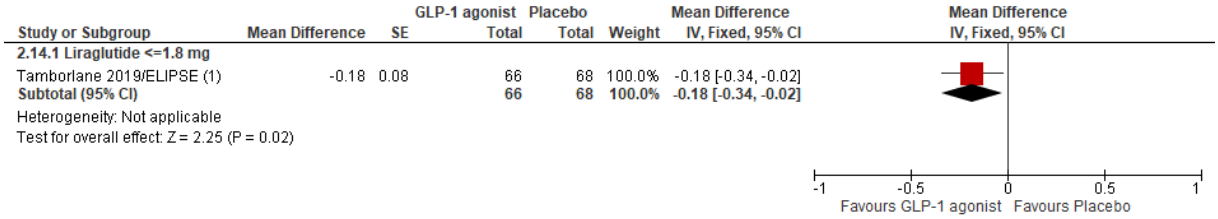
Fasting plasma glucose (mmol/L) – change score



Footnotes

(1) Maximum daily dose. Participants from weeks 26 to 52 discontinued placebo but continued metformin (with or without insulin) from weeks 0-26.

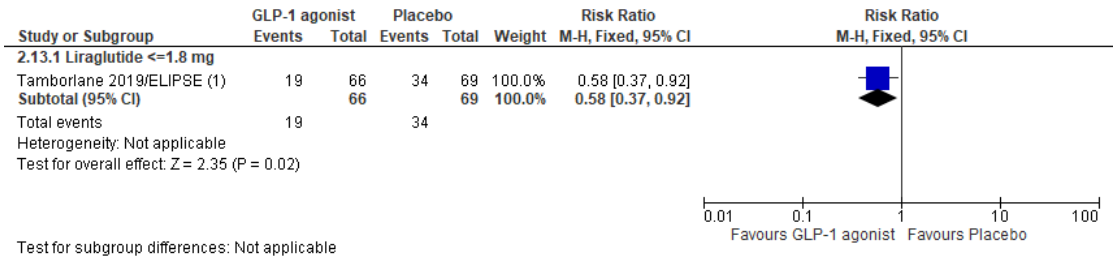
BMI z-score – change score



Footnotes

(1) Maximum daily dose. Participants from weeks 26 to 52 discontinued placebo but continued metformin (with or without insulin) from weeks 0-26.

Participants need rescue medication in form of insulin

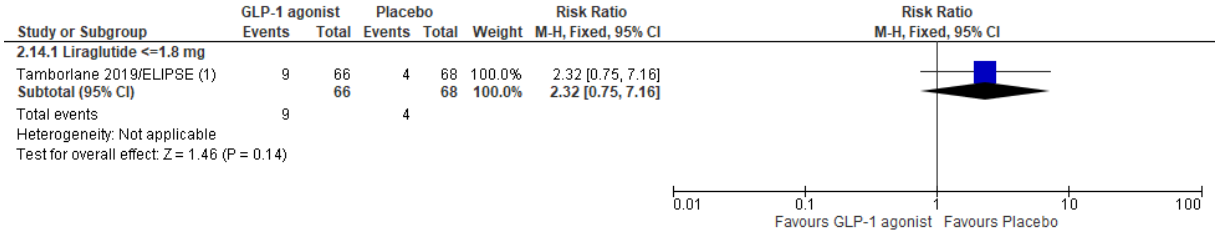


Test for subgroup differences: Not applicable

Footnotes

(1) Maximum daily dose. Participants from weeks 26 to 52 discontinued placebo but continued metformin (with or without insulin) from weeks 0-26.

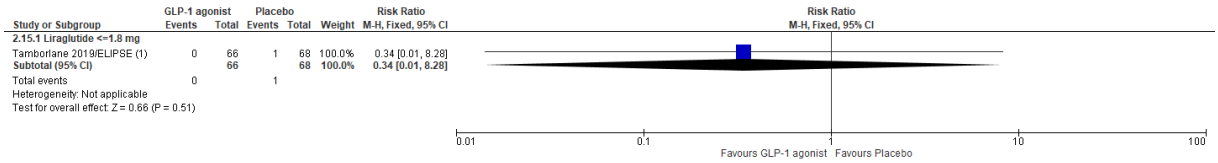
Serious adverse events



Footnotes

(1) 0-52 weeks. Maximum daily dose for 52 weeks. Participants from weeks 26 to 52 discontinued placebo but continued metformin (with or without insulin) from weeks 0-26.

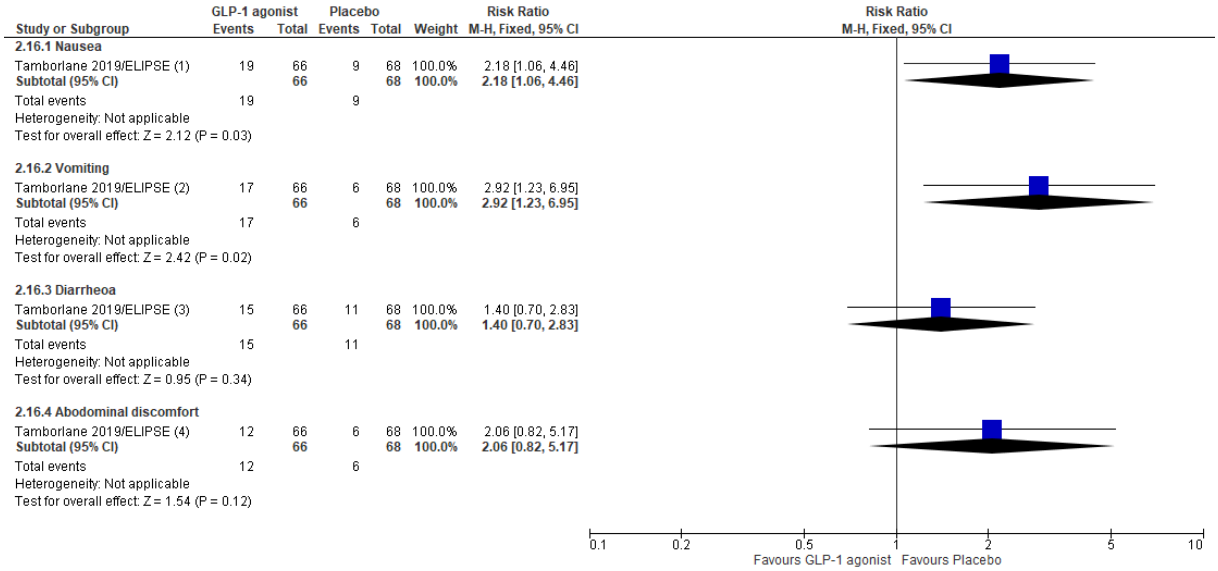
Severe hypoglycaemic episode



Footnotes

(1) 0-52 weeks. Maximum daily dose for 52 weeks. ADA classification of 'severe'=an episode requiring assistance of another person. Participants from weeks 26 to 52 discontinued placebo but continued metformin (with or without insulin) from weeks 0-26.

Other gastrointestinal symptoms

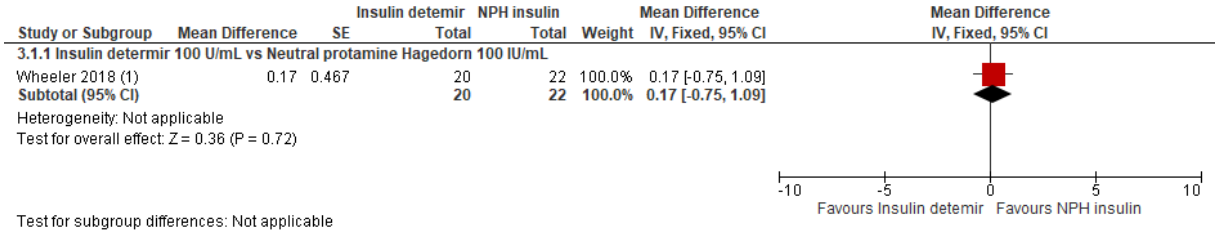


Footnotes

(1) 0-52 weeks. Liraglutide <=1.8 mg/day, maximum daily dose for 52 weeks. Participants from weeks 26 to 52 discontinued placebo but continued metformin (with or without insulin) from weeks 0-26.
(2) See note 1 above.
(3) See note 1 above.
(4) See note 1 above.

Short-term outcomes (≤26 weeks)

Glycated haemoglobin (HbA1c) % - change score



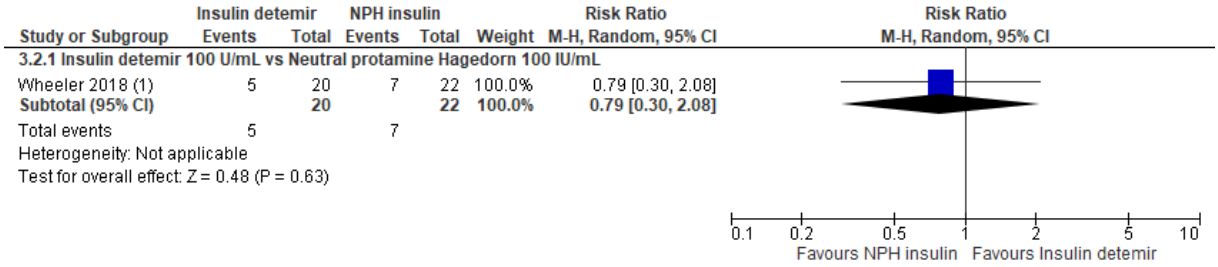
Test for subgroup differences: Not applicable

Footnotes

(1) Once or twice daily subcutaneous injection for 26 weeks.

Participants with glycated haemoglobin (HbA1c)≤<7.0%

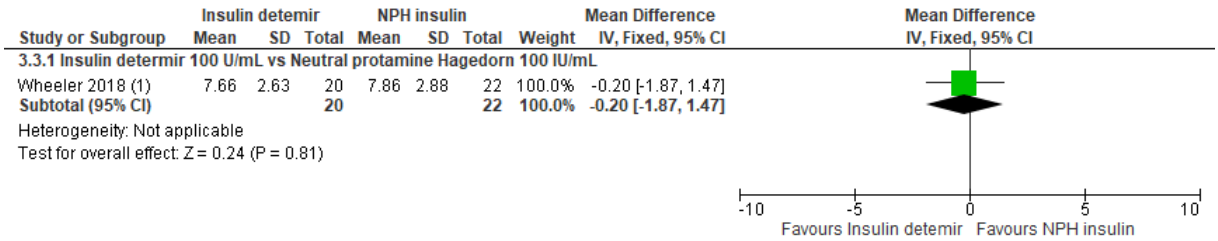
(RR more than 1 favours long-acting insulin regimen)



Footnotes

(1) Once or twice daily subcutaneous injection for 26 weeks. Number of participants HbA1c<7% at 26 weeks.

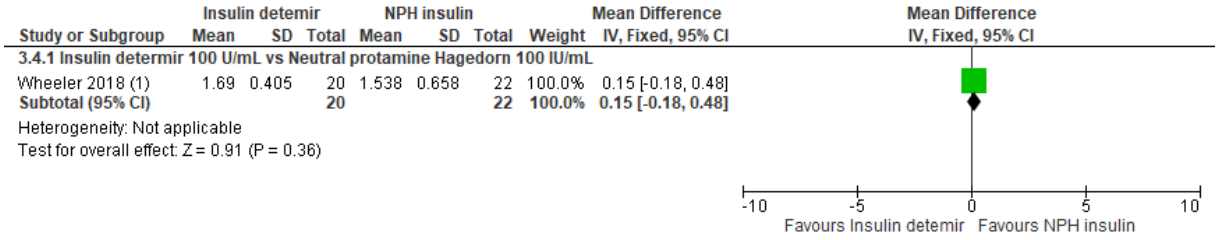
Fasting plasma glucose (mmol/L) – post-intervention score



Footnotes

(1) Once or twice daily subcutaneous injection for 26 weeks.

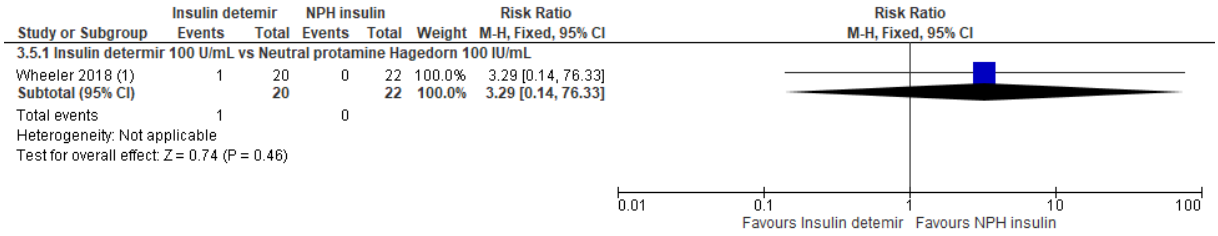
BMI z-score – post-intervention score



Footnotes

(1) Once or twice daily subcutaneous injection for 26 weeks.

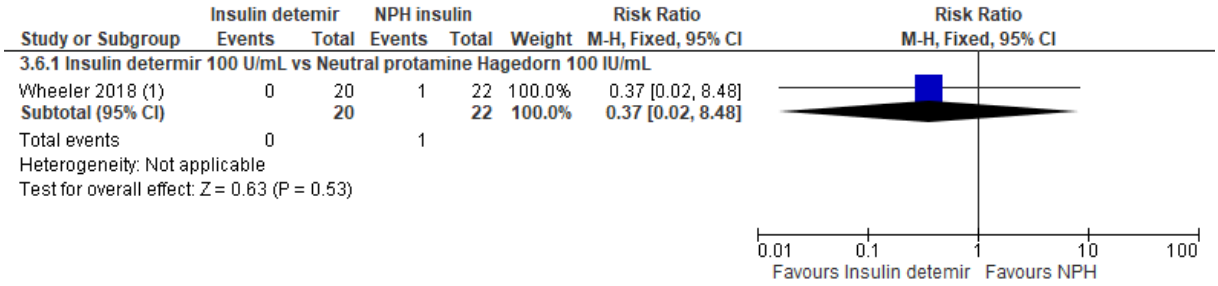
Participants need rescue medication in form of insulin



Footnotes

(1) 0-26 weeks. Once or twice daily subcutaneous injection. Participant did not comply with protocol resulting in persistent hyperglycaemia despite use of rescue medication.

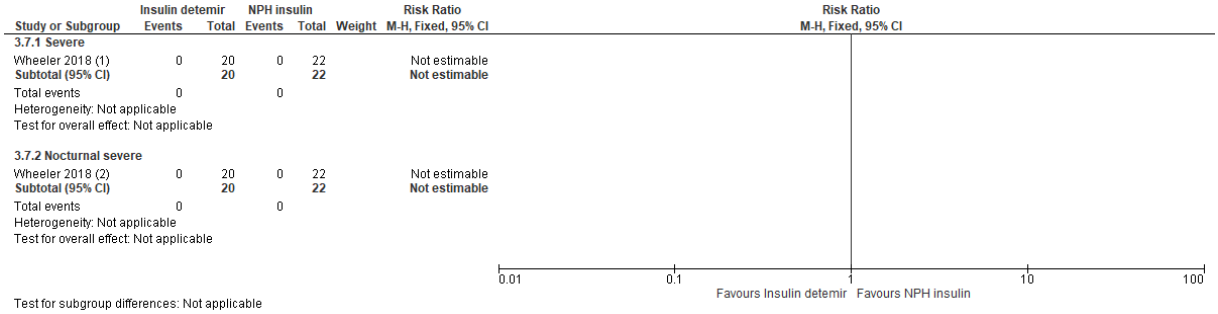
Serious adverse events



Footnotes

(1) 0-26 weeks. Once or twice daily subcutaneous injection for 26 weeks.

Severe hypoglycaemic episode



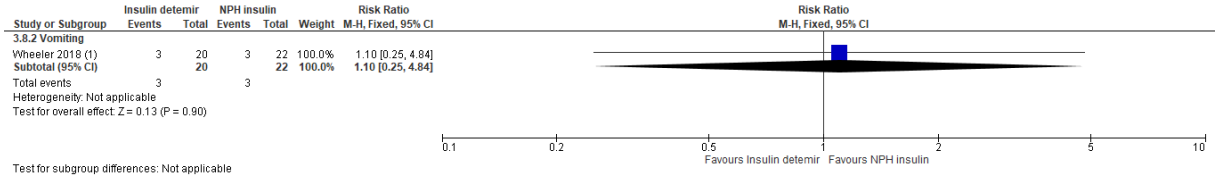
Test for subgroup differences: Not applicable

Footnotes

(1) 0-26 weeks. ADA classification of 'severe'=an episode requiring assistance of another person. Once or twice daily subcutaneous injection of either insulin detemir 100 U/mL or NPH insulin 100 IU/mL for 26 weeks.

(2) 'Nocturnal' defined as episodes reported with onset time between 11pm and 6.30am. See note 1 above.

Other gastrointestinal symptoms



Test for subgroup differences: Not applicable

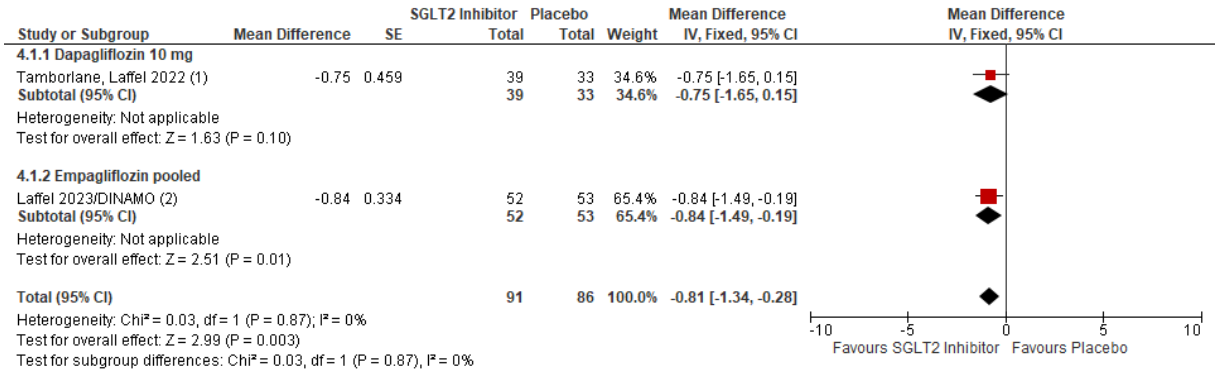
Footnotes

(1) 0-26 weeks. Study reports only that 10-15% of participants in each group experienced vomiting, assumed upper limit here.Once or twice daily subcutaneous injection of either insulin detemir 100 U/mL or NPH insulin 100 IU/mL for 26 weeks.

SGLT2 inhibitor vs Placebo

Short-term outcomes (≤26 weeks)

Glycated haemoglobin (HbA1c) % - change score



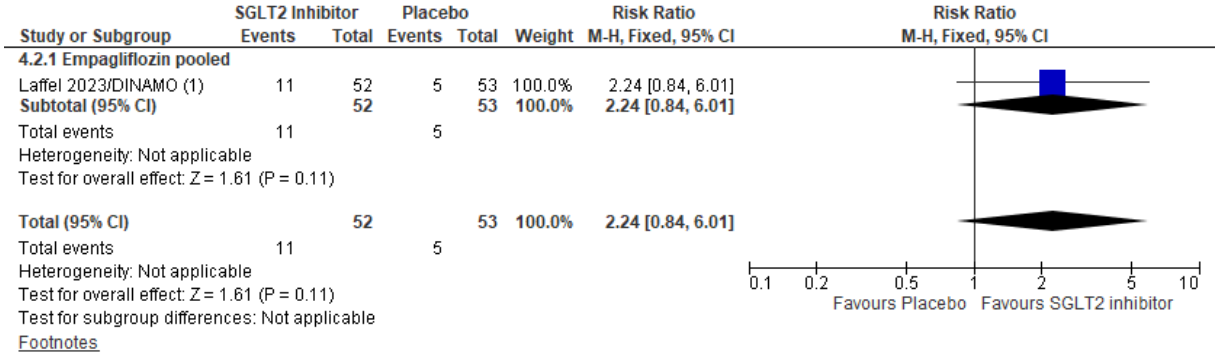
Footnotes

(1) Once daily for 24 weeks. Number of participants HbA1c<7% at 24 weeks. Study participants include 26% adults (18-24 years-old).

(2) 0-26 weeks. Empagliflozin 10 mg. Participants with HbA1c>=7% by week 12 randomised at week 14 to empagliflozin 10 mg or 25 mg.

Participants with glycated haemoglobin (HbA1c)<6.5%

(RR more than 1 favours SGLT2 inhibitor)

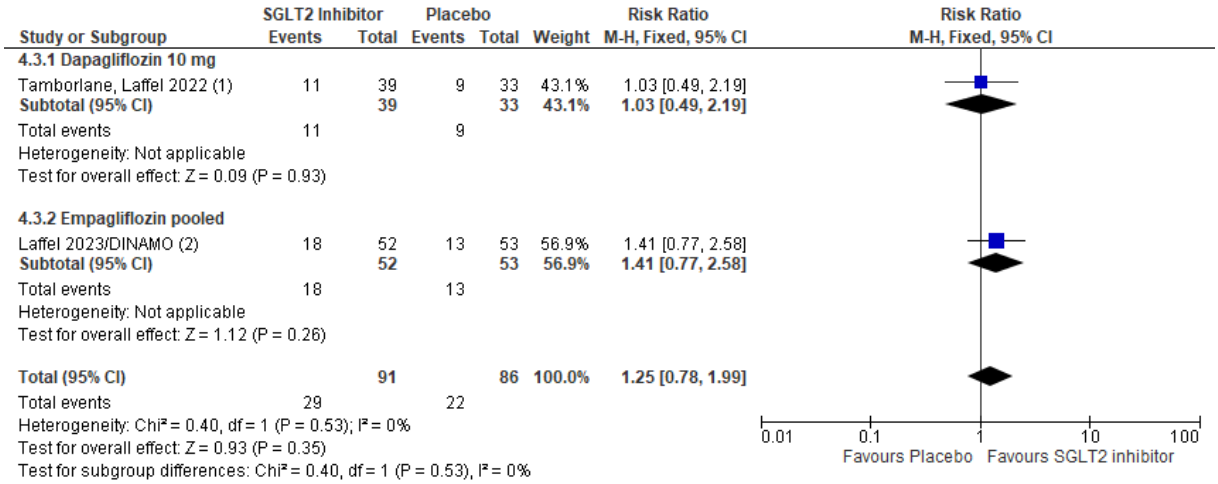


Footnotes

(1) 0-26 weeks. Empagliflozin 10 mg. Participants with HbA1c>=7% by week 12 randomised at week 14 to empagliflozin 10 mg or 25 mg.

Participants with glycated haemoglobin (HbA1c)<7.0%

(RR more than 1 favours SGLT2 inhibitor)

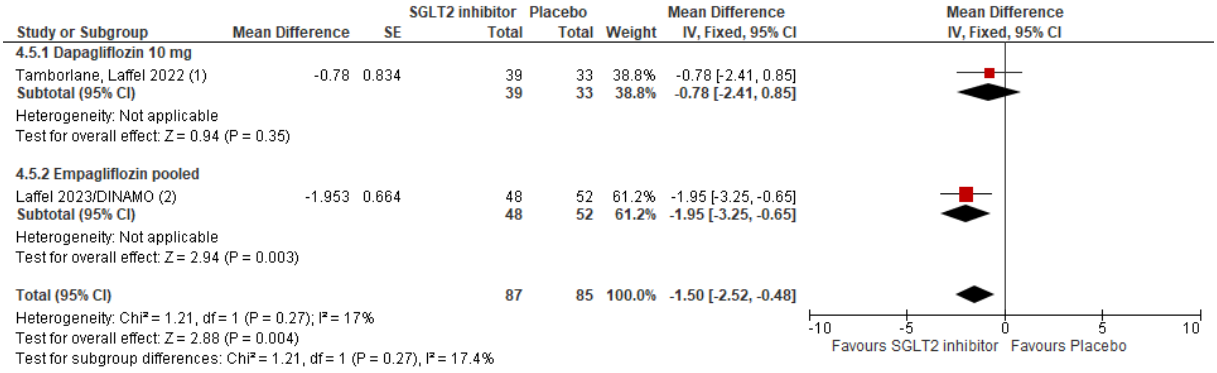


Footnotes

(1) Once daily for 24 weeks. Number of participants HbA1c<7% at 24 weeks. Study participants include 26% adults (18-24 years-old).

(2) 0-26 weeks. Empagliflozin 10 mg. Participants with HbA1c>=7% by week 12 randomised at week 14 to empagliflozin 10 mg or 25 mg.

Fasting plasma glucose (mmol/L) – change score

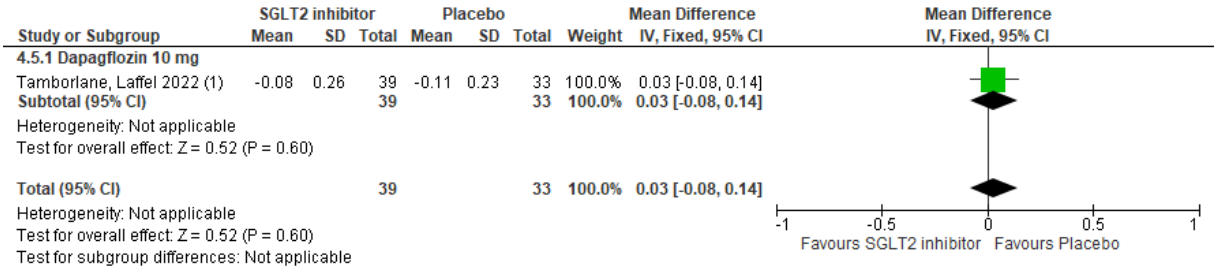


Footnotes

(1) Once daily for 24 weeks. Number of participants HbA1c<7% at 24 weeks. Study participants include 26% adults (18-24 years-old).

(2) 0-26 weeks. Empagliflozin 10 mg. Participants with HbA1c>=7% by week 12 randomised at week 14 to empagliflozin 10 mg or 25 mg.

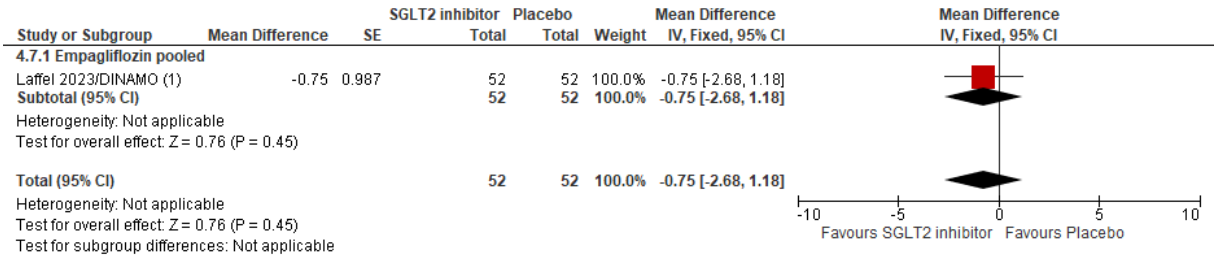
BMI z-score



Footnotes

(1) Change from baseline at 24 weeks. Once daily for 24 weeks. Study participants include 26% adults (18-24 years-old).

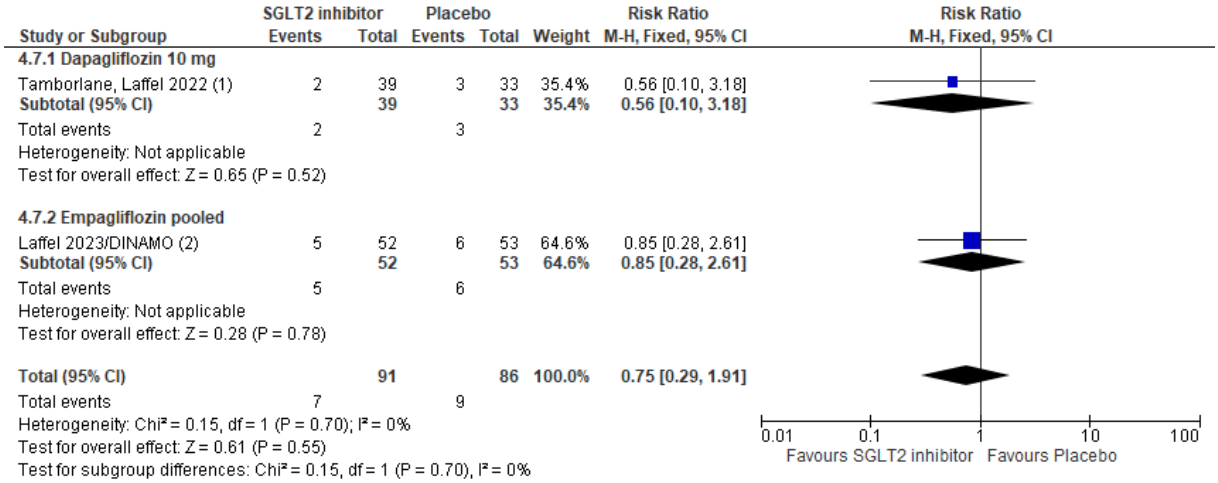
Weight (kg)



Footnotes

(1) 0-26 weeks. Empagliflozin 10 mg. Participants with HbA1c>=7% by week 12 randomised at week 14 to empagliflozin 10 mg or 25 mg.

Participants needing rescue medication in form of insulin

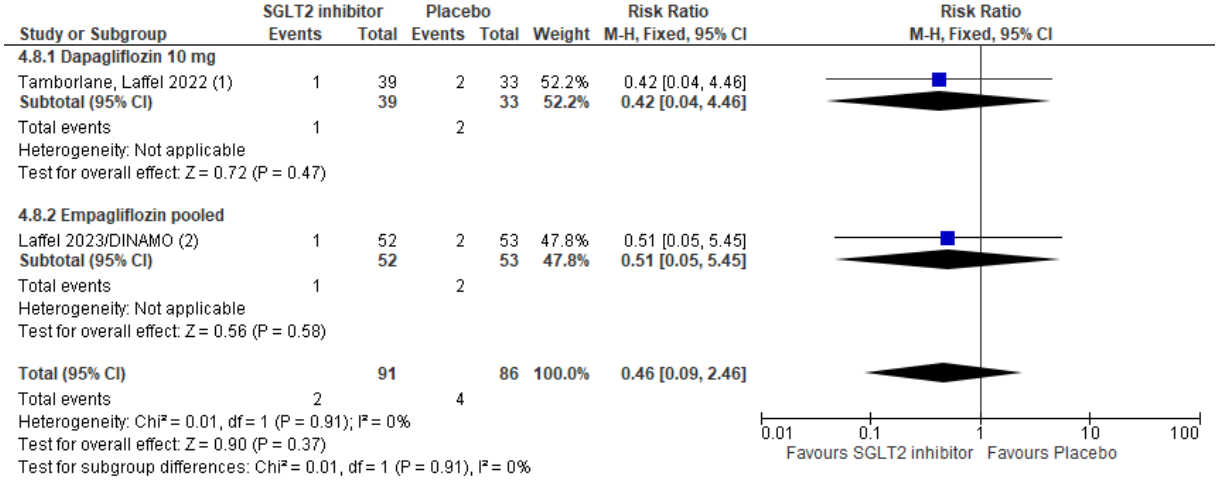


Footnotes

(1) 0-24 weeks. Once daily for 24 weeks. Study participants include 26% adults (18-24 years-old).

(2) 0-26 weeks. Empagliflozin 10 mg. Participants with HbA1c>=7% by week 12 randomised at week 14 to empagliflozin 10 mg or 25 mg.

Serious adverse events

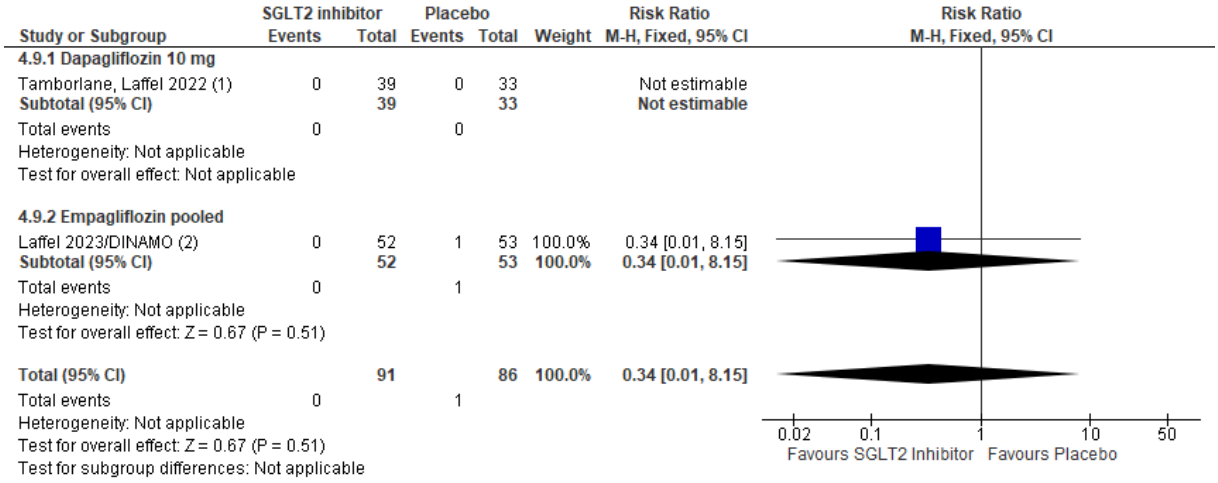


Footnotes

(1) 0-24 weeks. Once daily for 24 weeks. Study participants include 26% adults (18-24 years-old).

(2) 0-26 weeks. Empagliflozin 10 mg. Participants with HbA1c>=7% by week 12 randomised at week 14 to empagliflozin 10 mg or 25 mg.

Diabetic ketoacidosis/Hyperosmolar Hyperglycaemic State

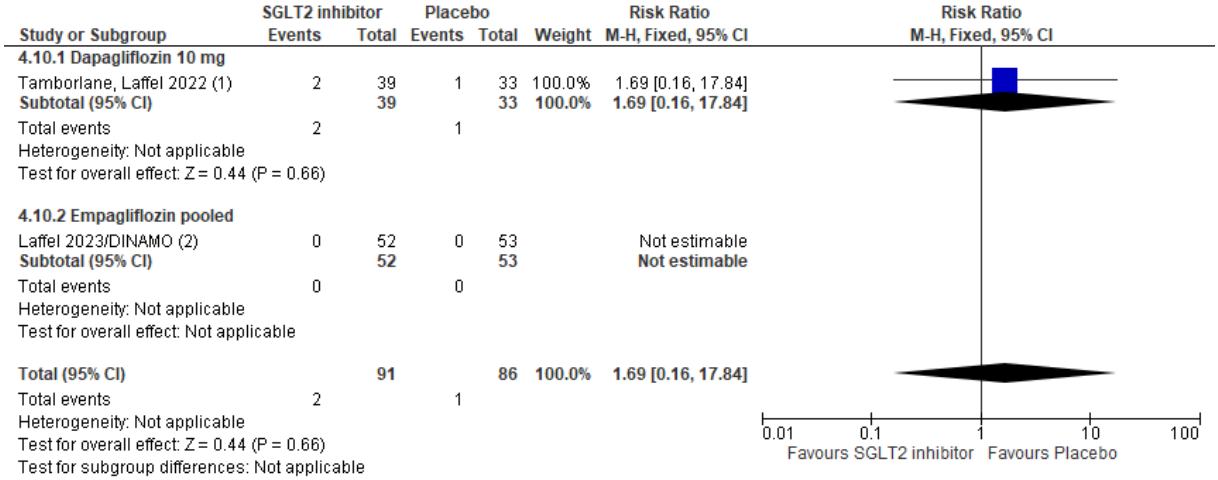


Footnotes

(1) 0-24 weeks. Reports no episodes of diabetic ketoacidosis. Once daily for 24 weeks. Study participants include 26% adults (18-24 years-old).

(2) 0-26 weeks. Empagliflozin 10 mg. Participants with HbA1c>=7% by week 12 randomised at week 14 to empagliflozin 10 mg or 25 mg.

Severe hypoglycaemic episode

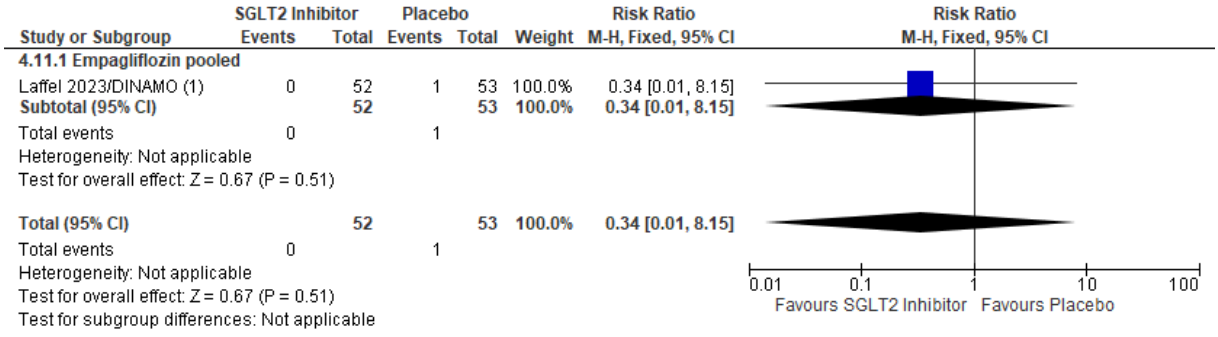


Footnotes

(1) 0-24 weeks. Once daily for 24 weeks. ADA classification of 'severe'=an episode requiring assistance of another person. Study participants include 26%...

(2) 0-26 weeks. Empagliflozin 10 mg. Participants with HbA1c>=7% by week 12 randomised at week 14 to empagliflozin 10 mg or 25 mg.

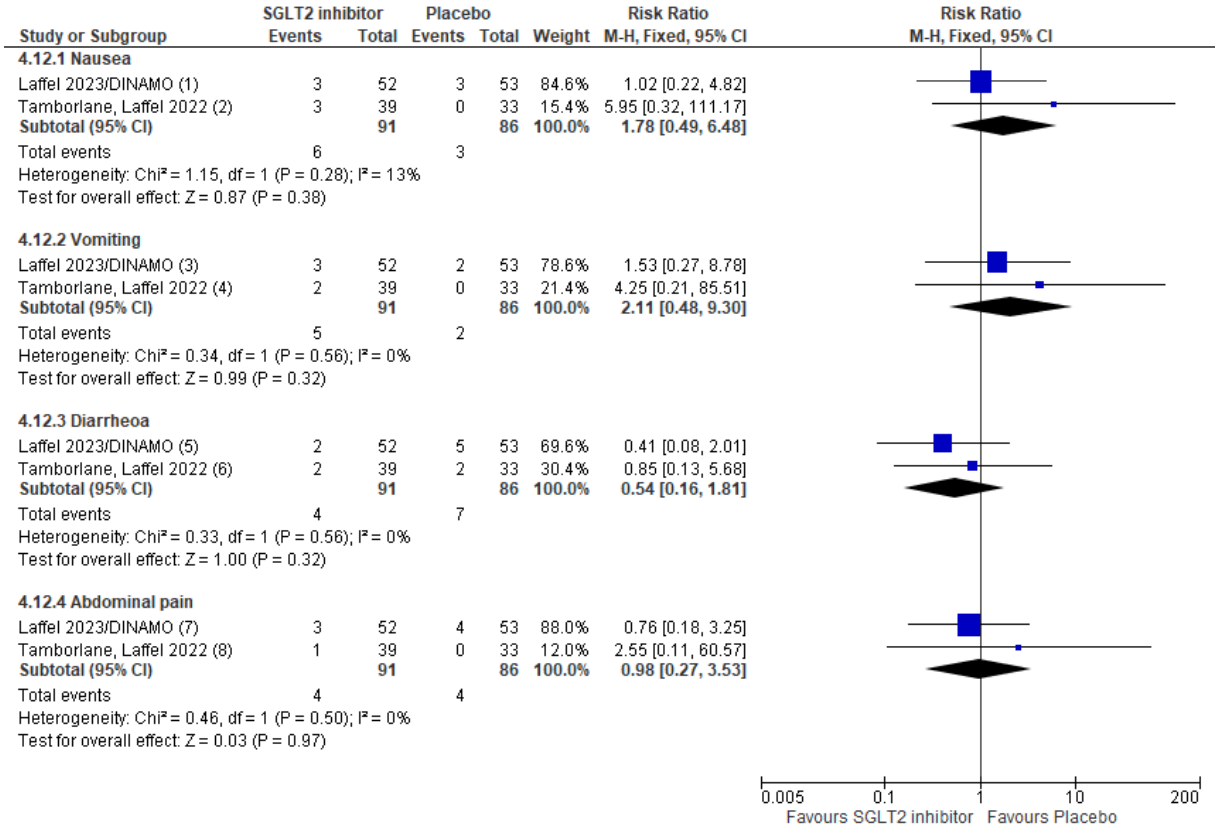
Pancreatitis



Footnotes

(1) 0-26 weeks. Empagliflozin 10 mg. Participants with HbA1c>=7% by week 12 randomised at week 14 to empagliflozin 10 mg or 25 mg.

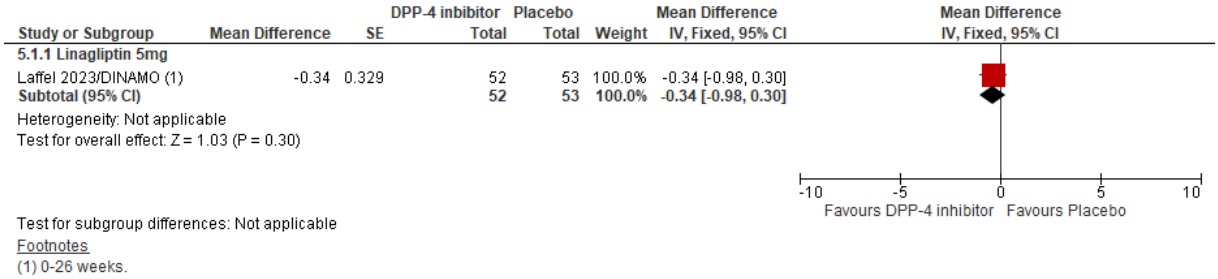
Other gastrointestinal symptoms



Footnotes

(1) 0-26 weeks. Empagliflozin 10 mg. Participants with HbA1c>=7% by week 12 randomised at week 14 to empagliflozin 10 mg or 25 mg.
(2) 0-24 weeks. Once daily dapagliflozin 10 mg for 24 weeks. Study participants include 26% adults (18-24 years-old).
(3) See note 1 above.
(4) See note 2 above.
(5) See note 1 above.
(6) See note 2 above.
(7) See note 1 above.
(8) See note 2 above.

Glycated haemoglobin (HbA1c) (%) – change score



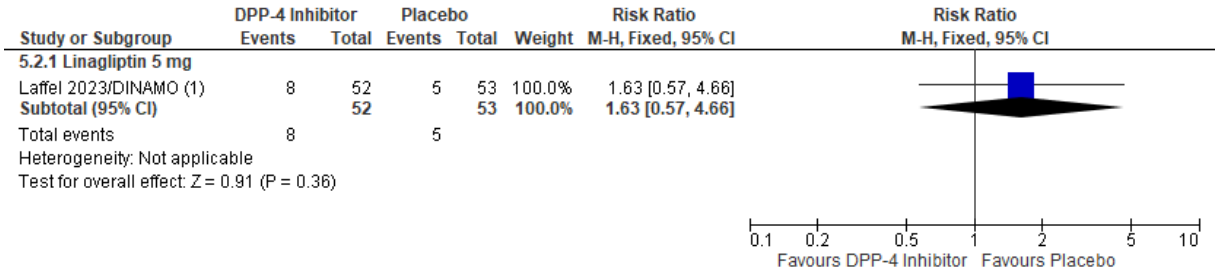
Test for subgroup differences: Not applicable

Footnotes

(1) 0-26 weeks.

Participants with glycated haemoglobin (HbA1c)<6.5%

(RR more than 1 favours SGLT2 inhibitor)

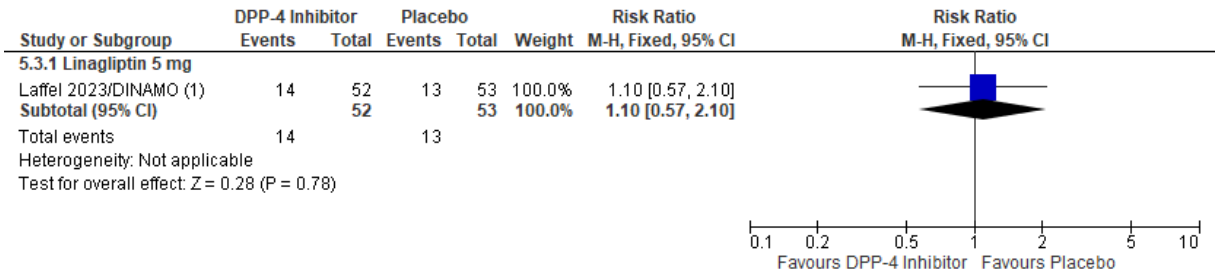


Footnotes

(1) 0-26 weeks.

Participants with glycated haemoglobin (HbA1c)<7.0%

(RR more than 1 favours SGLT2 inhibitor)



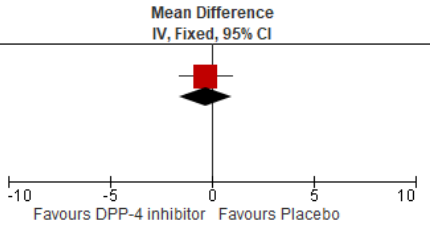
Footnotes

(1) 0-26 weeks.

Fasting plasma glucose (mmol/L) – change score

Study or Subgroup	Mean Difference	SE	Experimental Total	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
5.4.1 Linagliptin 5 mg						
Laffel 2023/DINAMO (1)	-0.3	0.654	51	52	100.0%	-0.30 [-1.58, 0.98]
Subtotal (95% CI)			**51**	**52**	**100.0%**	**-0.30 [-1.58, 0.98]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.46 (P = 0.65)



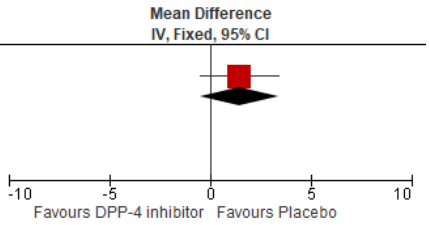
Test for subgroup differences: Not applicable

Footnotes
(1) 0-26 weeks.

Weight (kg)

Study or Subgroup	Mean Difference	SE	DPP-4 inhibitor Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
5.5.1 Linagliptin 5mg						
Laffel 2023/DINAMO (1)	1.46	0.992	50	52	100.0%	1.46 [-0.48, 3.40]
Subtotal (95% CI)			**50**	**52**	**100.0%**	**1.46 [-0.48, 3.40]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.47 (P = 0.14)



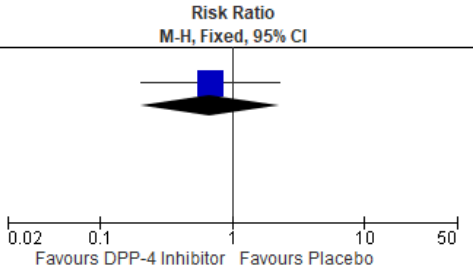
Test for subgroup differences: Not applicable

Footnotes
(1) 0-26 weeks.

Participants needing rescue medication in form of insulin

Study or Subgroup	DPP-4 Inhibitor Events	DPP-4 Inhibitor Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.6.1 Linagliptin 5 mg						
Laffel 2023/DINAMO (1)	4	52	6	53	100.0%	0.68 [0.20, 2.27]
Subtotal (95% CI)		**52**		**53**	**100.0%**	**0.68 [0.20, 2.27]**
Total events	4		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.63 (P = 0.53)

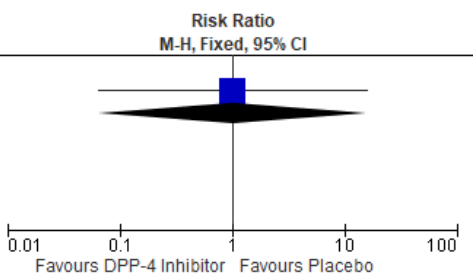


Footnotes
(1) 0-26 weeks.

Serious adverse events

Study or Subgroup	DPP-4 Inhibitor Events	DPP-4 Inhibitor Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.7.1 Linagliptin 5 mg						
Laffel 2023/DINAMO (1)	1	52	1	53	100.0%	1.02 [0.07, 15.87]
Subtotal (95% CI)		**52**		**53**	**100.0%**	**1.02 [0.07, 15.87]**
Total events	1		1			

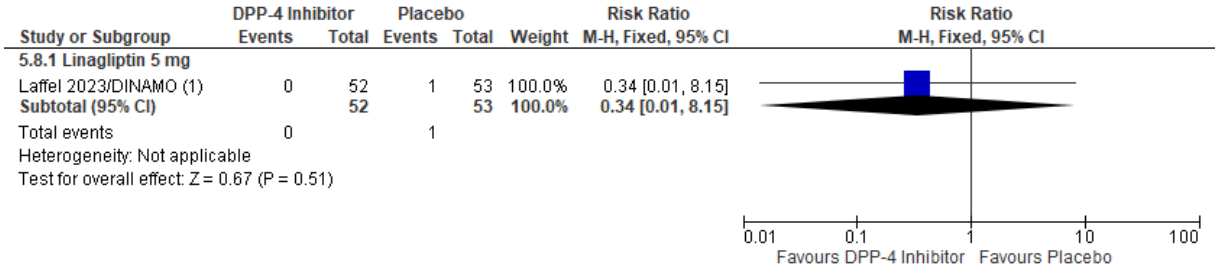
Heterogeneity: Not applicable
Test for overall effect: Z = 0.01 (P = 0.99)



Test for subgroup differences: Not applicable

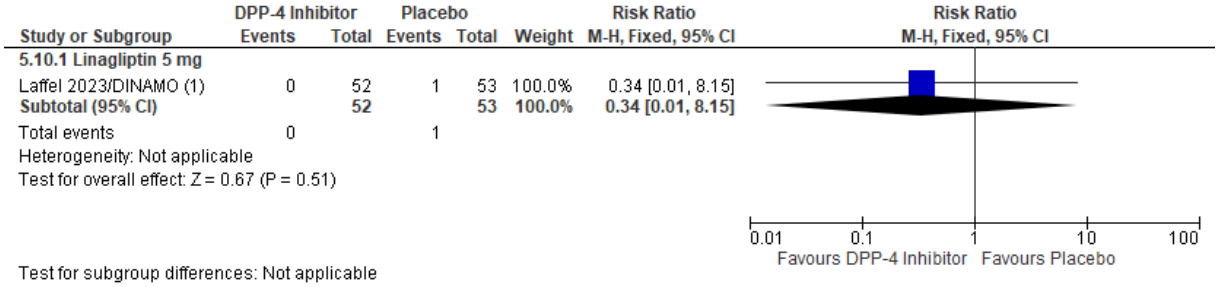
Footnotes
(1) 0-26 weeks.

Diabetic ketoacidosis/Hyperosmolar Hyperglycaemic State



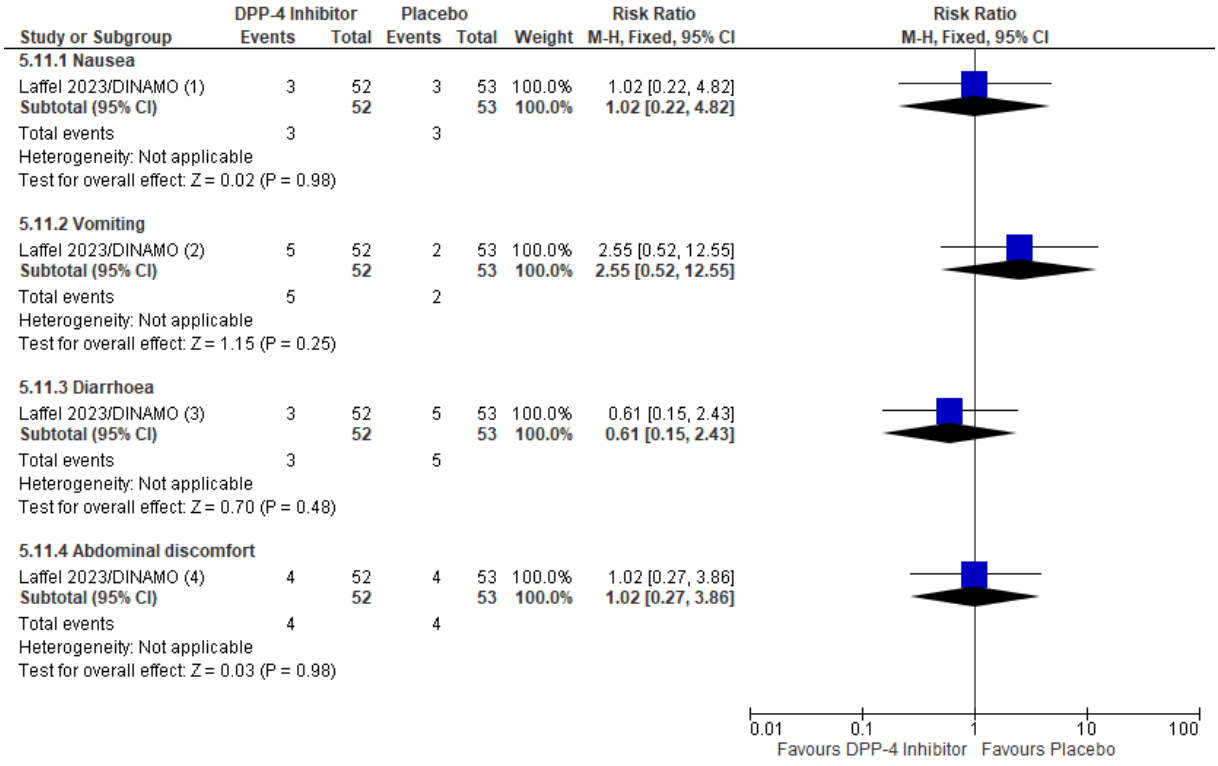
Footnotes
(1) 0-26 weeks.

Pancreatitis



Test for subgroup differences: Not applicable
Footnotes
(1) 0-26 weeks.

Other gastrointestinal symptoms

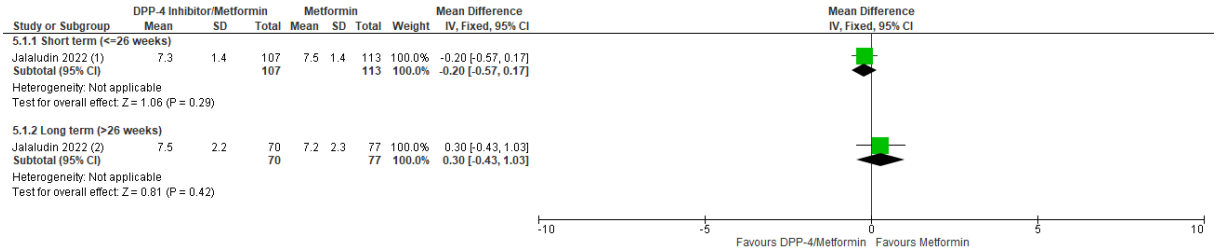


Footnotes
(1) 0-26 weeks.Linagliptin 5 mg vs Placebo, 3-arm trial.
(2) See above footnote.
(3) See above footnote.
(4) See above footnote. Reported as 'abdominal pain'.

DPP-4 inhibitor (Sitagliptin) + Metformin vs Metformin

Short (≤26 weeks) and long-term (>26 weeks) outcomes

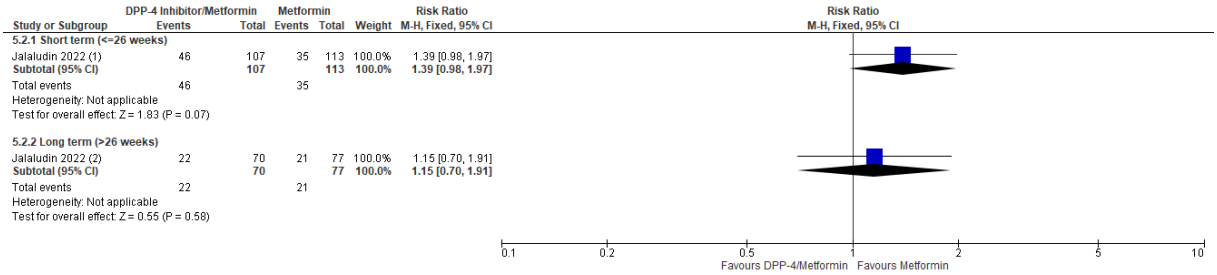
Glycated haemoglobin (HbA1c) % - post-intervention score



Footnotes
(1) Pooled data from 2 trials: twice daily FDC .sitagliptin 50 mg and immediate-release metformin or once daily FDC sitagliptin 100 mg and extended-release metformin, in addition to ongoing metformin +/- insulin therapy, for 20 weeks.
(2) As above for 54 weeks.

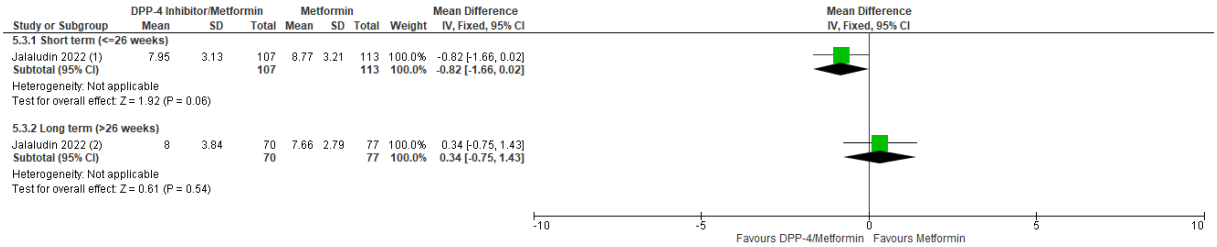
Participants with glycated haemoglobin (HbA1c)<7.0%

(RR>1 favours DPP-4/Metformin)



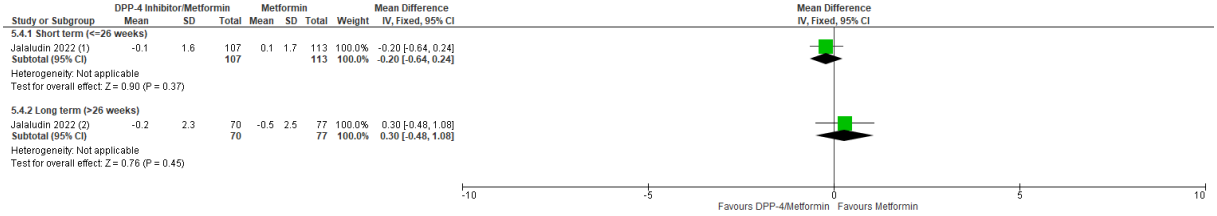
Footnotes
(1) Pooled data from 2 trials: twice daily FDC of sitagliptin 50 mg and immediate-release metformin or once daily FDC of sitagliptin 100 mg and extended-release metformin, in addition to ongoing metformin +/- insulin therapy, for 20 weeks.
(2) As above for 54 weeks.

Fasting plasma glucose (mmol/L) – post-intervention score



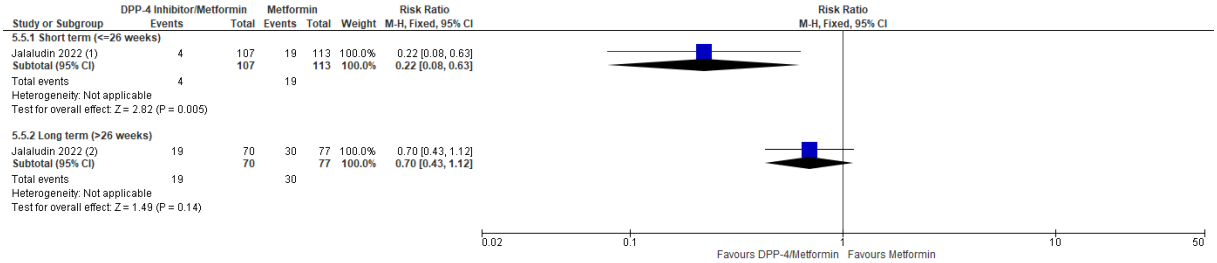
Footnotes
(1) Pooled data from 2 trials: twice daily FDC of sitagliptin 50 mg and immediate-release metformin or once daily FDC of sitagliptin 100 mg and extended-release metformin, in addition to ongoing metformin +/- insulin therapy, for 20 weeks.
(2) As above for 54 weeks.

BMI (kg/m^2) – change score



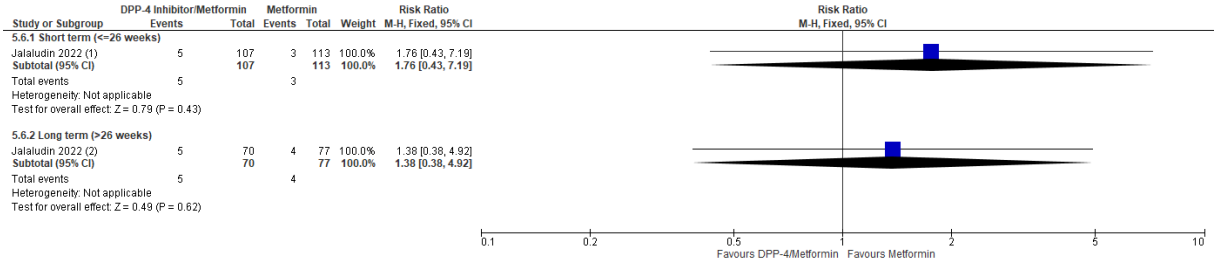
Footnotes
(1) Change from baseline at 20 weeks. Pooled data from 2 trials: twice daily FDC of sitagliptin 50 mg and immediate-release metformin or once daily FDC of sitagliptin 100 mg and extended-release metformin, in addition to ongoing metformin +/- insulin therapy, for 20 weeks.
(2) Change from baseline at 54 weeks. As above for 54 weeks.

Participants needing rescue medication in form of insulin



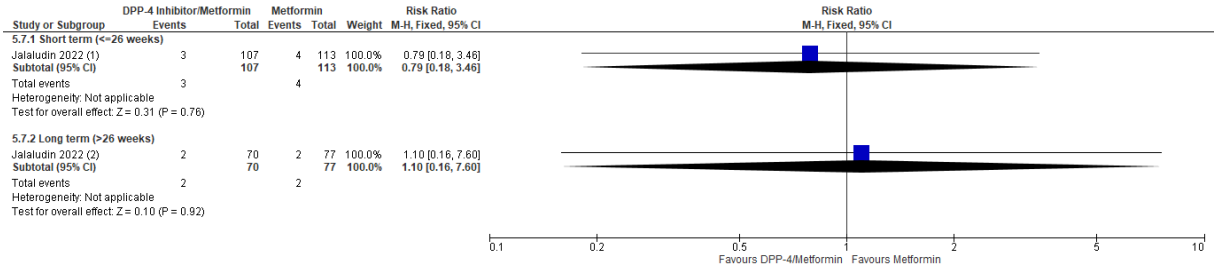
Footnotes
(1) 0-20 weeks. Pooled data from 2 trials: twice daily FDC of sitagliptin 50 mg and immediate-release metformin or once daily FDC of sitagliptin 100 mg and extended-release metformin, in addition to ongoing metformin +/- insulin therapy, for 20 weeks.
(2) 0-54 weeks. As above for 54 weeks.

Serious adverse events



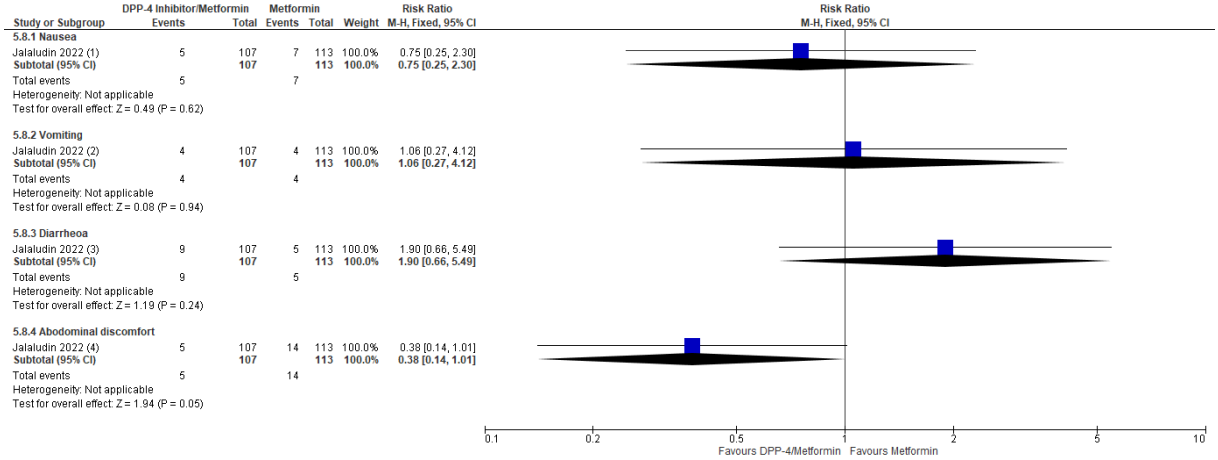
Footnotes
(1) 0-20 weeks. Pooled data from 2 trials: twice daily FDC of sitagliptin 50 mg and immediate-release metformin or once daily FDC of sitagliptin 100 mg and extended-release metformin, in addition to ongoing metformin +/- insulin therapy, for 20 weeks.
(2) 0-54 weeks. As above for 54 weeks.

Severe hypoglycaemic episode



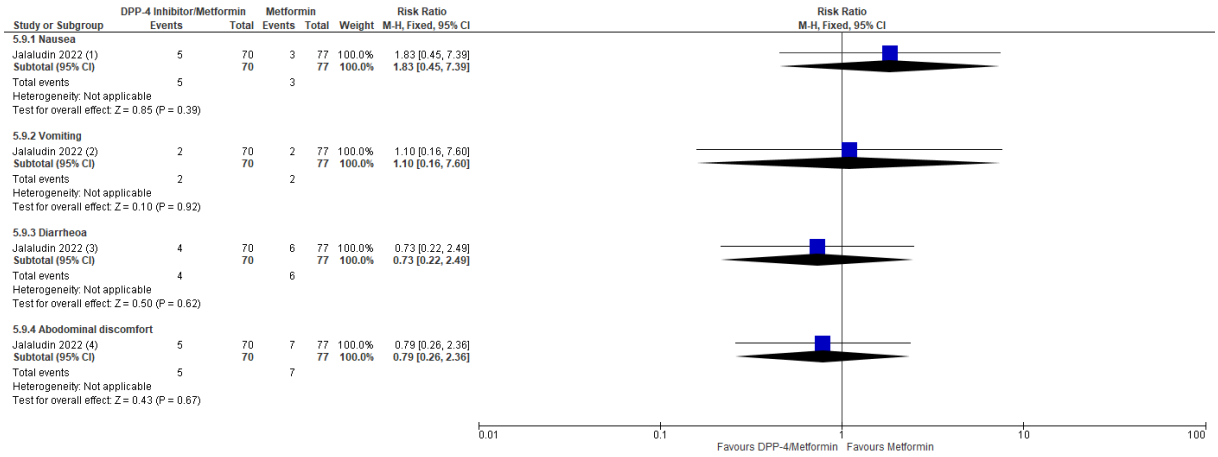
Footnotes
(1) 0-20 weeks. 'Severe'=symptomatic episode requiring medical/non-medical assistance. Pooled data from 2 trials: twice daily FDC sitagliptin 50 mg/immediate-release metformin or once daily FDC sitagliptin 100 mg/extended-release metformin.
(2) 0-54 weeks. As above for 54 weeks.

Other gastrointestinal symptoms – Short term (≤26 weeks)



Footnotes
(1) 0-20 weeks. Pooled data from 2 trials: twice daily FDC of sitagliptin 50 mg and immediate-release metformin or once daily FDC of sitagliptin 100 mg and extended-release metformin, in addition to ongoing metformin +/- insulin therapy for 20 weeks.
(2) See note 1 above.
(3) See note 1 above.
(4) Includes lower abdominal pain, upper abdominla pain, abdominal pain, abdominbal discomfort, and epigastric discomfort. See note 1 above.

Other gastrointestinal symptoms – Long term (>26 weeks)



Footnotes
(1) 0-54 weeks. Pooled data from 2 trials: twice daily FDC of sitagliptin 50 mg and immediate-release metformin or once daily FDC of sitagliptin 100 mg and extended-release metformin, in addition to ongoing metformin +/- insulin therapy, for 54 weeks.
(2) See note 1 above.
(3) See note 1 above.
(4) Includes lower abdominal pain, upper abdominla pain, abdominal pain, abdominbal discomfort, and epigastric discomfort. See note 1 above.

Appendix F – GRADE tables

Second-line treatment

DPP-4 inhibitor vs Placebo then Metformin

Table 9: Full GRADE table for DPP-4 inhibitor vs Placebo then Metformin

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**DPP-4 inhibitor**	**Placebo then Metformin**	**Relative (95% CI)**	**Absolute (95% CI)**		
Glycated haemoglobin % - Short-term change score (≤26 weeks) (follow-up: 20 weeks; assessed with: HbA1c blood test)												
1	randomised trials	serious[a]	not serious	not serious	serious[b,c]	none	95	95	-	MD **0.3 lower** (0.77 lower to 0.17 higher)	⨁⨁◯◯ Low	CRITICAL
Glycated haemoglobin % - Long-term post-intervention score (>26 weeks) (follow-up: 54 weeks; assessed with: HbA1c blood test)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**DPP-4 inhibitor**	**Placebo then Metformin**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious[a]	not serious	not serious	serious[b,c]	none	95	90	-	MD **0.6 higher** (0.18 higher to 1.02 higher)	⊕⊕◯◯ Low	CRITICAL
Participants with HbA1c<7% - Short term (≤26 weeks) (follow-up: 20 weeks; assessed with: HbA1c blood test)												
1	randomised trials	serious[a]	not serious	not serious	serious[d]	none	47/95 (49.5%)	35/95 (36.8%)	**RR 1.34** (0.96 to 1.87)	**125 more per 1,000** (from 15 fewer to 321 more)	⊕⊕◯◯ Low	CRITICAL
Participants with HbA1c<7% - Long term (>26 weeks) (follow-up: 54 weeks; assessed with: HbA1c blood test)												
1	randomised trials	serious[a]	not serious	not serious	serious[d]	none	27/95 (28.4%)	36/95 (37.9%)	**RR 0.75** (0.50 to 1.13)	**95 fewer per 1,000** (from 189 fewer to 49 more)	⊕⊕◯◯ Low	CRITICAL
Fasting plasma glucose mmol/L - Short-term change score (≤26 weeks) (follow-up: 20 weeks; assessed with: FPG blood test)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**DPP-4 inhibitor**	**Placebo then Metformin**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious[a]	not serious	not serious	not serious[c]	none	95	95	-	MD **0.08 higher** (0.81 lower to 0.97 higher)	⊕⊕⊕◯ Moderate	CRITICAL
Fasting plasma glucose mmol/L - Long term post-intervention score (>26 weeks) (follow-up: 54 weeks; assessed with: FPG blood test)												
1	randomised trials	very serious[a]	not serious	not serious	not serious[c]	none	95	90	-	MD **0.45 higher** (0.21 lower to 1.11 higher)	⊕⊕◯◯ Low	CRITICAL
Serious adverse events - long term (>26 weeks) (follow-up: 54 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[e]	none	9/95 (9.5%)	4/95 (4.2%)	**RR 2.25** (0.72 to 7.06)	**53 more per 1,000** (from 12 fewer to 255 more)	⊕◯◯◯ Very low	IMPORTANT
Other gastrointestinal symptoms - short term ≤26 weeks) - Nausea (follow-up: 20 weeks; assessed with: Participant reported)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**DPP-4 inhibitor**	**Placebo then Metformin**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	very serious[a]	not serious	not serious	very serious[e]	none	5/95 (5.3%)	1/95 (1.1%)	**RR 5.0** (0.6 to 42.0)	**42 more per 1,000** (from 4 fewer to 432 more)	⊕◯◯◯ Very low	IMPORTANT
Other gastrointestinal symptoms - short term ≤26 weeks) - Vomiting (follow-up: 20 weeks; assessed with: Participant reported)												
1	randomised trials	serious[a]	not serious	not serious	very serious[e]	none	4/95 (4.2%)	2/95 (2.1%)	**RR 2.00** (0.38 to 10.66)	**21 more per 1,000** (from 13 fewer to 203 more)	⊕◯◯◯ Very low	IMPORTANT
Other gastrointestinal symptoms - short term ≤26 weeks) - Diarrhoea (assessed with: Participant reported)												
1	randomised trials	serious[a]	not serious	not serious	very serious[e]	none	3/95 (3.2%)	5/95 (5.3%)	**RR 0.60** (0.15 to 2.44)	**21 fewer per 1,000** (from 45 fewer to 76 more)	⊕◯◯◯ Very low	IMPORTANT
Other gastrointestinal symptoms - short term ≤26 weeks) - Abdominal discomfort (follow-up: 20 weeks; assessed with: Participant reported)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**DPP-4 inhibitor**	**Placebo then Metformin**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious[a]	not serious	not serious	very serious[e]	none	8/95 (8.4%)	9/95 (9.5%)	**RR 0.89** (0.36 to 2.21)	**10 fewer per 1,000** (from 61 fewer to 115 more)	⊕◯◯◯ Very low	IMPORTANT
Other gastrointestinal symptoms - long term (>26 weeks) - Nausea (follow-up: 54 weeks; assessed with: Participant reported)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[e]	none	5/95 (5.3%)	4/95 (4.2%)	**RR 1.25** (0.35 to 4.51)	**11 more per 1,000** (from 27 fewer to 148 more)	⊕◯◯◯ Very low	IMPORTANT
Other gastrointestinal symptoms - long term (>26 weeks) - Vomiting (follow-up: 54 weeks; assessed with: Participant reported)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[e]	none	6/95 (6.3%)	7/95 (7.4%)	**RR 0.86** (0.30 to 2.46)	**10 fewer per 1,000** (from 52 fewer to 108 more)	⊕◯◯◯ Very low	IMPORTANT
Other gastrointestinal symptoms - long term (>26 weeks) - Diarrhoea (follow-up: 20 weeks; assessed with: Participant reported)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**DPP-4 inhibitor**	**Placebo then Metformin**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	very serious[a]	not serious	not serious	very serious[e]	none	8/95 (8.4%)	11/95 (11.6%)	**RR 0.73** (0.31 to 1.73)	**31 fewer per 1,000** (from 80 fewer to 85 more)	⊕◯◯◯ Very low	IMPORTANT
Other gastrointestinal symptoms - long term (>26 weeks) - Abdominal discomfort (follow-up: 54 weeks; assessed with: Participant reported)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[e]	none	11/95 (11.6%)	13/95 (13.7%)	**RR 0.85** (0.40 to 1.79)	**21 fewer per 1,000** (from 82 fewer to 108 more)	⊕◯◯◯ Very low	IMPORTANT

Unless otherwise stated, continuous outcomes with MD<0 and dichotomous outcomes with RR<1 favour intervention.

Abbreviations: BMI, body mass index; DPP-4, dipeptidyl peptidase-4; FPG, fasting plasma glucose; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; mmol/L, millimoles per litre.

Notes

a. For short-term outcomes, downgraded by 1 level because trial was at high risk of bias due to serious concerns about randomisation (no information about process and differences between groups in baseline characteristics). For long-term outcomes, downgraded by 2 levels because in addition, there were some concerns about missing data (high proportion of missing long-term data).
b. Downgraded 1 level because 95% CI crosses 1 MID for this outcome.
c. MID for HbA1c %: +/- 0.5%. MIDs, calculated as 0.5 median SD of the comparison group, for the following outcomes are: Fasting plasma glucose (short term)=+/-3.11; Fasting plasma glucose (long term)=+/-1.12.
d. Downgraded 1 level because 95% CI crosses 1 default MID for relative risk outcomes.

e. Downgraded 2 levels because 95% CI crosses 2 default MIDs for relative risk outcomes.

Metformin combination therapy

GLP-1 receptor agonist vs Placebo

Table 10: Full GRADE table for GLP-1 receptor agonist vs Placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**GLP-1 agonist**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Glycated haemoglobin % - short-term change score (≤26 weeks) (follow-up: range 24 weeks to 26 weeks; assessed with: HbA1c blood test)												
3	randomised trials	serious[a]	not serious	serious[b]	not serious[c]	none	227	143	-	MD **1.14 lower** (1.48 lower to 0.79 lower)	⊕⊕◯◯ Low	CRITICAL
Glycated haemoglobin % - short-term change score (≤26 weeks) - Dulaglutide 0.75 mg or 1.5 mg (follow-up: 26 weeks; assessed with: HbA1c blood test)												
1	randomised trials	serious[d]	not serious	serious[e]	not serious[c]	none	103	51	-	MD **1.4 lower** (1.95 lower to 0.85 lower)	⊕⊕◯◯ Low	CRITICAL
Glycated haemoglobin % - short-term change score (≤26 weeks) - Exenatide 2mg (follow-up: 24 weeks; assessed with: HbA1c blood test)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**GLP-1 agonist**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious[d]	not serious	serious[e]	serious[c,f]	none	58	24	-	MD **0.85 lower** (1.51 lower to 0.19 lower)	⨁◯◯◯ Very low	CRITICAL
Glycated haemoglobin % - short-term change score (≤26 weeks) - Liraglutide ≤1.8 mg (follow-up: 26 weeks; assessed with: HbA1c blood test)												
1	randomised trials	not serious	not serious	not serious	serious[c,f]	none	66	68	-	MD **1.06 lower** (1.66 lower to 0.46 lower)	⨁⨁⨁◯ Moderate	CRITICAL
Participants with HbA1c≤6.5% - short term (≤26 weeks) (follow-up: 26 weeks; assessed with: HbA1c blood test)												
2	randomised trials	serious[a]	not serious	serious[e]	not serious	none	43/161 (26.7%)	5/75 (6.7%)	**RR 4.24** (1.92 to 9.37)	**216 more per 1,000** (from 61 more to 558 more)	⨁⨁◯◯ Low	CRITICAL
Participants with HbA1c≤6.5% - short term (≤26 weeks) - Dulaglutide 0.75 mg or 1.5 mg (follow-up: 26 weeks; assessed with: HbA1c blood test)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**GLP-1 agonist**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious[d]	not serious	serious[e]	not serious	none	-/103	-/51	**RR 4.26** (1.80 to 10.09)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕◯◯ Low	CRITICAL
Participants with HbA1c≤6.5% - short term (≤26 weeks) - Exenatide 2 mg (follow-up: 24 weeks; assessed with: HbA1c blood test)												
1	randomised trials	serious[d]	not serious	serious[e]	very serious[g]	none	-/58	-/24	**RR 4.14** (0.56 to 30.57)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ Very low	CRITICAL
Participants with HbA1c<7% - short term (≤26 weeks) (follow-up: range 24 weeks to 26 weeks; assessed with: HbA1c blood test)												
3	randomised trials	serious[a]	serious[h]	serious[b]	not serious	none	109/227 (48.0%)	33/143 (23.1%)	**RR 2.67** (1.25 to 5.68)	**385 more per 1,000** (from 58 more to 1,000 more)	⊕◯◯◯ Very low	CRITICAL
Participants with HbA1c<7% - short term (≤26 weeks) - Dulaglutide 0.75 mg or 1.5 mg (follow-up: 26 weeks; assessed with: HbA1c blood test)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**GLP-1 agonist**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious[d]	not serious	serious[e]	not serious	none	53/103 (51.5%)	7/51 (13.7%)	**RR 3.75** (1.84 to 7.65)	**377 more per 1,000** (from 115 more to 913 more)	⊕⊕◯◯ Low	CRITICAL
Participants with HbA1c<7% - short term (≤26 weeks) - Exenatide 2 mg (follow-up: 24 weeks; assessed with: HbA1c blood test)												
1	randomised trials	serious[d]	not serious	serious[e]	serious[f]	none	14/58 (24.1%)	1/24 (4.2%)	**RR 5.79** (0.81 to 41.63)	**200 more per 1,000** (from 8 fewer to 1,000 more)	⊕◯◯◯ Very low	CRITICAL
Participants with HbA1c<7% - short term (≤26 weeks) - Liraglutide ≤1.8 mg (follow-up: 26 weeks; assessed with: HbA1c blood test)												
1	randomised trials	not serious	not serious	not serious	very serious[f]	none	42/66 (63.6%)	25/68 (36.8%)	**RR 1.73** (1.21 to 2.48)	**268 more per 1,000** (from 77 more to 544 more)	⊕⊕◯◯ Low	CRITICAL
Subgroup analysis: HbA1c<7% - short term (26 weeks) - Overall (follow-up: range 24 weeks to 26 weeks; assessed with: HbA1c blood test)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**GLP-1 agonist**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
2	randomised trials	serious[a]	not serious	serious[e]	not serious	none	67/161 (41.6%)	8/75 (10.7%)	**RR 3.94** (2.02 to 7.71)	**314 more per 1,000** (from 109 more to 716 more)	⊕⊕◯◯ Low	CRITICAL
Fasting plasma glucose mmol/L - short-term change score (≤26 weeks) (follow-up: range 24 weeks to 26 weeks; assessed with: FPG blood test)												
3	randomised trials	serious[a]	not serious	serious[e]	not serious[c]	none	227	143	-	MD **1.8 lower** (2.48 lower to 1.11 lower)	⊕⊕◯◯ Low	CRITICAL
Fasting plasma glucose mmol/L - short-term change score (≤26 weeks) - Dulaglutide 0.75 mg or 1.5 mg (follow-up: 26 weeks; assessed with: FPG blood test)												
1	randomised trials	serious[d]	not serious	serious[e]	not serious[c]	none	103	51	-	MD **2 lower** (3 lower to 1 lower)	⊕⊕◯◯ Low	CRITICAL
Fasting plasma glucose mmol/L - short-term change score (≤26 weeks) - Exenatide 2 mg (follow-up: 24 weeks; assessed with: FPG blood test)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**GLP-1 agonist**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious[d]	not serious	serious[e]	not serious[c]	none	58	24	-	MD **1.2 lower** (2.72 lower to 0.32 higher)	⊕⊕◯◯ Low	CRITICAL
Fasting plasma glucose mmol/L - short-term change score (≤26 weeks) - Liraglutide ≤1.8 mg (follow-up: 26 weeks; assessed with: FPG blood test)												
1	randomised trials	not serious	not serious	not serious	not serious[c]	none	66	68	-	MD **1.88 lower** (3.1 lower to 0.66 lower)	⊕⊕⊕⊕ High	CRITICAL
BMI z-score - short-term change score (≤26 weeks) (follow-up: 26 weeks)												
2	randomised trials	serious[a]	not serious	serious[b]	not serious[c]	none	169	119	-	MD **0.05 lower** (0.15 lower to 0.05 higher)	⊕⊕◯◯ Low	CRITICAL
BMI z-score - short-term change score (≤26 weeks) - Dulaglutide 0.75 mg or 1.5 mg (follow-up: 26 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**GLP-1 agonist**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious[d]	not serious	serious[e]	not serious[c]	none	103	51	-	MD **0.01 lower** (0.56 lower to 0.54 higher)	⊕⊕◯◯ Low	CRITICAL
BMI z-score - short-term change score (≤26 weeks) - Liraglutide ≤1.8 mg (follow-up: 26 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious[c]	none	66	68	-	MD **0.05 lower** (0.15 lower to 0.05 higher)	⊕⊕⊕⊕ High	CRITICAL
Participants needing rescue medication in form of insulin - short term (≤26 weeks) (follow-up: range 24 weeks to 26 weeks)												
3	randomised trials	serious[a]	not serious	serious[b]	not serious	none	13/227 (5.7%)	31/144 (21.5%)	**RR 0.35** (0.20 to 0.63)	**140 fewer per 1,000** (from 172 fewer to 80 fewer)	⊕⊕◯◯ Low	CRITICAL
Participants needing rescue medication in form of insulin - short term (≤26 weeks) - Dulaglutide 0.75 mg or 1.5 mg (follow-up: 26 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**GLP-1 agonist**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious[d]	not serious	serious[e]	not serious	none	3/103 (2.9%)	9/51 (17.6%)	**RR 0.17** (0.05 to 0.58)	**146 fewer per 1,000** (from 168 fewer to 74 fewer)	⊕⊕◯◯ Low	CRITICAL
Participants needing rescue medication in form of insulin - short term (≤26 weeks) - Exenatide 2 mg (follow-up: 24 weeks)												
1	randomised trials	serious[d]	not serious	serious[e]	very serious[g]	none	1/58 (1.7%)	0/24 (0.0%)	**RR 1.27** (0.05 to 30.15)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ Very low	CRITICAL
Participants needing rescue medication in form of insulin - short term (≤26 weeks) - Liraglutide ≤1.8 mg (follow-up: 26 weeks)												
1	randomised trials	not serious	not serious	not serious	serious[i]	none	9/66 (13.6%)	22/69 (31.9%)	**RR 0.43** (0.21 to 0.86)	**182 fewer per 1,000** (from 252 fewer to 45 fewer)	⊕⊕⊕◯ Moderate	CRITICAL
Serious adverse events - short term (≤26 weeks) (follow-up: range 24 weeks to 26 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**GLP-1 agonist**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
2	randomised trials	serious[a]	not serious	serious[b]	very serious[g]	none	4/162 (2.5%)	4/74 (5.4%)	**RR 0.45** (0.11 to 1.78)	**30 fewer per 1,000** (from 48 fewer to 42 more)	⊕◯◯◯ Very low	IMPORTANT
Serious adverse events - short term (≤26 weeks) - Dulaglutide 0.75 mg or 1.5 mg (follow-up: 26 weeks)												
1	randomised trials	serious[d]	not serious	serious[e]	very serious[g]	none	2/103 (1.9%)	3/51 (5.9%)	**RR 0.33** (0.06 to 1.91)	**39 fewer per 1,000** (from 55 fewer to 54 more)	⊕◯◯◯ Very low	IMPORTANT
Serious adverse events - short term (≤26 weeks) - Exenatide 2 mg (follow-up: 24 weeks)												
1	randomised trials	serious[d]	not serious	serious[e]	very serious[g]	none	2/59 (3.4%)	1/23 (4.3%)	**RR 0.78** (0.07 to 8.19)	**10 fewer per 1,000** (from 40 fewer to 313 more)	⊕◯◯◯ Very low	IMPORTANT
Severe hypoglycaemic episode - short term (≤26 weeks) (follow-up: range 24 weeks to 26 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**GLP-1 agonist**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
2	randomised trials	serious[d]	not serious	serious[e]	very serious[g]	none	1/162 (0.6%)	0/74 (0.0%)	**RR 1.20** (0.05 to 28.44)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	IMPORTANT
Severe hypoglycaemic episode - short term (≤26 weeks) - Dulaglutide 0.75 mg or 1.5 mg (follow-up: 26 weeks)												
1	randomised trials	serious[d]	not serious	serious[e]		none	0/103 (0.0%)	0/51 (0.0%)	not estimable		-	IMPORTANT
Severe hypoglycaemic episode - short term (≤26 weeks) - Exenatide 2 mg (follow-up: 24 weeks)												
1	randomised trials	serious[d]	not serious	not serious	very serious[g]	none	1/59 (1.7%)	0/23 (0.0%)	**RR 1.20** (0.05 to 28.44)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	IMPORTANT
Pancreatitis - short term (≤26 weeks) - Dulaglutide 0.75 mg or 1.5 mg (follow-up: 26 weeks)												
1	randomised trials	serious[d]	not serious	serious[e]		none	0/103 (0.0%)	0/51 (0.0%)	not estimable		-	IMPORTANT
Other gastrointestinal symptoms - short term (≤26 weeks) - Nausea (follow-up: 26 weeks; assessed with: Participant reported)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**GLP-1 agonist**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
2	randomised trials	serious	not serious	serious[e]	very serious[g]	none	19/162 (11.7%)	5/74 (6.8%)	**RR 1.79** (0.70 to 4.60)	**53 more per 1,000** (from 20 fewer to 243 more)	⨁◯◯◯ Very low	IMPORTANT
Other gastrointestinal symptoms - short term (≤26 weeks) - Vomiting (follow-up: 26 weeks; assessed with: Participant reported)												
2	randomised trials	serious	not serious	serious[e]	serious[i]	none	19/162 (11.7%)	2/74 (2.7%)	**RR 3.72** (1.03 to 13.41)	**74 more per 1,000** (from 1 more to 335 more)	⨁◯◯◯ Very low	IMPORTANT
Other gastrointestinal symptoms - short term (≤26 weeks) - Diarrhoea (follow-up: 26 weeks; assessed with: Participant reported)												
2	randomised trials	serious[a]	not serious	serious[e]	very serious[g]	none	24/162 (14.8%)	8/74 (10.8%)	**RR 1.42** (0.67 to 3.01)	**45 more per 1,000** (from 36 fewer to 217 more)	⨁◯◯◯ Very low	IMPORTANT
Other gastrointestinal symptoms - short term (≤26 weeks) - Abdominal discomfort (follow-up: 26 weeks; assessed with: Participant reported)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**GLP-1 agonist**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
2	randomised trials	serious	not serious	serious[e]	very serious[g]	none	7/162 (4.3%)	6/74 (8.1%)	**RR 0.53** (0.19 to 1.51)	**38 fewer per 1,000** (from 66 fewer to 41 more)	⊕◯◯◯ Very low	IMPORTANT
Glycated haemoglobin % - long-term change score (>26 weeks) - Liraglutide ≤1.8 mg (follow-up: 54 weeks; assessed with: HbA1c blood test)												
1	randomised trials	serious[j]	not serious	not serious	not serious	none	66	68	-	MD **1.3 lower** (1.9 lower to 0.7 lower)	⊕⊕⊕◯ Moderate	IMPORTANT
Fasting plasma glucose mmol/L - long-term change score (>26 weeks) - Liraglutide ≤1.8 mg (follow-up: 54 weeks; assessed with: FPG blood test)												
1	randomised trials	serious[j]	not serious	not serious	not serious[c]	none	66	68	-	MD **1.81 lower** (3.18 lower to 0.44 lower)	⊕⊕⊕◯ Moderate	IMPORTANT
BMI z-score - long-term change score (>26 weeks) - Liraglutide ≤1.8 mg (follow-up: 54 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**GLP-1 agonist**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious[j]	not serious	not serious	not serious[c]	none	66	68	-	MD **0.18 lower** (0.34 lower to 0.02 lower)	⨁⨁⨁◯ Moderate	IMPORTANT
Participants needing rescue medication in form of insulin - long term (>26 weeks) - Liraglutide ≤1.8 mg (follow-up: 54 weeks)												
1	randomised trials	serious[j]	not serious	not serious	serious[i]	none	19/66 (28.8%)	34/69 (49.3%)	**RR 0.58** (0.37 to 0.92)	**207 fewer per 1,000** (from 310 fewer to 39 fewer)	⨁⨁◯◯ Low	IMPORTANT
Serious adverse events - long term (>26 weeks) - Liraglutide ≤1.8 mg (follow-up: 54 weeks)												
1	randomised trials	serious[j]	not serious	not serious	very serious[g]	none	9/66 (13.6%)	4/68 (5.9%)	**RR 2.32** (0.75 to 7.16)	**78 more per 1,000** (from 15 fewer to 362 more)	⨁◯◯◯ Very low	IMPORTANT
Severe hypoglycaemic episode - long term (>26 weeks) - Liraglutide ≤1.8 mg (follow-up: 54 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**GLP-1 agonist**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious[j]	not serious	not serious	very serious[g]	none	0/66 (0.0%)	1/68 (1.5%)	**RR 0.34** (0.01 to 8.28)	**10 fewer per 1,000** (from 15 fewer to 107 more)	⊕◯◯◯ Very low	IMPORTANT
Other gastrointestinal symptoms - long term (>26 weeks) - Nausea (follow-up: 54 weeks; assessed with: Participant reported)												
1	randomised trials	serious[j]	not serious	not serious	serious[i]	none	19/66 (28.8%)	9/68 (13.2%)	**RR 2.18** (1.06 to 4.46)	**156 more per 1,000** (from 8 more to 458 more)	⊕⊕◯◯ Low	IMPORTANT
Other gastrointestinal symptoms - long term (>26 weeks) - Vomiting (follow-up: 54 weeks; assessed with: Participant reported)												
1	randomised trials	serious[j]	not serious	not serious	serious[i]	none	17/66 (25.8%)	6/68 (8.8%)	**RR 2.92** (1.23 to 6.95)	**169 more per 1,000** (from 20 more to 525 more)	⊕⊕◯◯ Low	IMPORTANT
Other gastrointestinal symptoms - long term (>26 weeks) - Diarrhoea (follow-up: 54 weeks; assessed with: Participant reported)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**GLP-1 agonist**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious[j]	not serious	not serious	very serious[g]	none	15/66 (22.7%)	11/68 (16.2%)	**RR 1.40** (0.70 to 2.83)	**65 more per 1,000** (from 49 fewer to 296 more)	⨁◯◯◯ Very low	IMPORTANT
Other gastrointestinal symptoms - long term (>26 weeks) - Abodominal discomfort (follow-up: 54 weeks; assessed with: Participant reported)												
1	randomised trials	serious[j]	not serious	not serious	serious[i]	none	12/66 (18.2%)	6/68 (8.8%)	**RR 2.06** (0.82 to 5.17)	**94 more per 1,000** (from 16 fewer to 368 more)	⨁⨁◯◯ Low	IMPORTANT

Unless otherwise stated, continuous outcomes with MD<0 and dichotomous outcomes with RR<1 favour intervention.

Abbreviations: BMI, body mass index; DPP-4, dipeptidyl peptidase-4; FDC, fixed-dose combination; FPG, fasting plasma glucose; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; IU/mL, international units per millilitre; mg, milligram; mmol/L, millimoles per litre; ng/mL, nanograms per millilitre; U/ml, units per millilitre; SGLT2, Sodium-glucose co-transporter-2; T2DM, Type 2 diabetes mellitus.

Notes
a. Downgraded by 1 level because >33% of the weight from meta-analysis is from trial(s) that is at moderate risk of bias due to concerns about the randomisation process (no information provided and/or baseline differences between groups).
b. Downgraded by 1 level because >33% of the weight from meta-analysis are trials that include participants not on metformin.
c. MID for HbA1c %: +/- 0.5%. MIDs, calculated as 0.5 median SD of the comparison group, for the following outcomes are: Fasting plasma glucose (short term) - overall: +/-3.35; Fasting plasma glucose (short term) - dulaglutide: +/- 3.14; Fasting plasma glucose (short term) - exenatide: +/-3.46; Fasting plasma glucose (short term) - liraglutide: +/-3.57; Fasting

plasma glucose (long term) - liraglutide: +/-4.01; BMI z-score (short term) - overall: +/-0.33; BMI z-score (short term) - dulaglutide: +/- 0.98; BMI z-score (short term) - liraglutide: +/- 0.34; BMI z-score (long term) - liraglutide: +/- 0.44.
d. Downgraded by 1 level because there were some concerns about the randomisation process (no information provided and/or baseline differences between groups).
e. Downgraded by 1 level because 100% of the weight from meta-analysis are trials that included participants who were not receiving metformin therapy: Duraglutide (Arslanian 2022: 22%); Exenatide (Tamborlane and Bishai 2022: 9%).
f. Downgraded by 1 level because 95% CI crosses 1 MID for this outcome.
g. Downgraded by 2 levels because 95% CI crosses 2 MIDs for this type of outcome.
h. Downgraded by 1 level because there is high heterogeneity (i2>50%-80%) in the overall results and between subgroups.
i. Downgraded by 1 level because 95% CI crosses 1 MID for this type of outcome.
j. Downgraded by 1 level because there are some concerns about lack of blinding for long-term outcomes (which were assessed during a 26-week open-label period, weeks 26-54) .

Table 11: Full GRADE table for Long-acting insulin regimen vs Intermediate-acting insulin regimen

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Long-acting insulin regimen**	**Intermediate-acting insulin regimen**	**Relative (95% CI)**	**Absolute (95% CI)**		
Glycated haemoglobin % - short term (≤26 weeks) - Insulin detemir 100 U/mL vs Neutral protamine Hagedorn insulin 100 IU/mL (follow-up: 26 weeks; assessed with: HbA1c blood test)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b,c]	none	20	22	-	MD **0.17 higher** (0.75 lower to 1.09 higher)	⊕◯◯◯ Very low	CRITICAL
Participants with HbA1c<7% - short term (≤26 weeks) - Insulin detemir 100 U/mL vs Neutral protamine Hagedorn insulin 100 IU/mL (follow-up: 26 weeks; assessed with: HbA1c blood test)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	5/20 (25.0%)	7/22 (31.8%)	**RR 0.79** (0.30 to 2.08)	**67 fewer per 1,000** (from 223 fewer to 344 more)	⊕◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Long-acting insulin regimen**	**Intermediate-acting insulin regimen**	**Relative (95% CI)**	**Absolute (95% CI)**		
Fasting plasma glucose mmol/L - short term (≤26 weeks) - Insulin detemir 100 U/mL vs Neutral protamine Hagedorn insulin 100 IU/mL (follow-up: 26 weeks; assessed with: FPG blood test)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b,c]	none	20	22	-	MD **0.2 lower** (1.87 lower to 1.47 higher)	⊕◯◯◯ Very low	CRITICAL
BMI z-score - short term (≤26 weeks) - Insulin detemir 100 U/mL vs Neutral protamine Hagedorn insulin 100 IU/mL (follow-up: 26 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	serious[c,d]	none	20	22	-	MD **0.15 higher** (0.18 lower to 0.48 higher)	⊕◯◯◯ Very low	CRITICAL
Participants needing rescue medication in form of insulin - short term (≤26 weeks) - Insulin detemir 100 U/mL vs Neutral protamine Hagedorn 100 IU/mL (follow-up: 26 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Long-acting insulin regimen**	**Intermediate-acting insulin regimen**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	1/20 (5.0%)	0/22 (0.0%)	**RR 3.29** (0.14 to 76.33)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ Very low	CRITICAL
Serious adverse events - short term (≤26 weeks) - Insulin detemir 100 U/mL vs Neutral protamine Hagedorn insulin 100 IU/mL (follow-up: 26 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	very serious	none	0/20 (0.0%)	1/22 (4.5%)	**RR 0.37** (0.02 to 8.48)	**29 fewer per 1,000** (from 45 fewer to 340 more)	⊕◯◯◯ Very low	IMPORTANT
Severe hypoglycaemic episode - short term (≤26 weeks) - Insulin detemir 100 U/mL vs Neutral protamine Hagedorn insulin 100 IU/mL (follow-up: 26 weeks)												
1	randomised trials	very serious[a]	not serious	not serious		none	0/20 (0.0%)	0/22 (0.0%)	not estimable		-	IMPORTANT
Nocturnal severe hypoglycaemic episode - short term (≤26 weeks) - Insulin detemir 100 U/mL vs Neutral protamine Hagedorn insulin 100 IU/mL (follow-up: 26 weeks; assessed with: Participant reported)												
1	randomised trials	very serious[a]	not serious	not serious		none	0/20 (0.0%)	0/22 (0.0%)	not estimable		-	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Long-acting insulin regimen**	**Intermediate-acting insulin regimen**	**Relative (95% CI)**	**Absolute (95% CI)**		
Other gastrointestinal symptoms - Vomiting (short term [≤26 weeks]) - Insulin detemir 100 U/mL vs Neutral protamine Hagedorn insulin 100 IU/mL (follow-up: 26 weeks; assessed with: Participant reported)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	3/20 (15.0%)	3/22 (13.6%)	**RR 1.10** (0.25 to 4.84)	**14 more per 1,000** (from 102 fewer to 524 more)	⊕◯◯◯ Very low	IMPORTANT

Unless otherwise stated, continuous outcomes with MD<0 and dichotomous outcomes with RR<1 favour intervention.

Abbreviations: BMI, body mass index; HbA1c, glycated haemoglobin; IU/mL, international units per millilitre; mmol/L, millimoles per litre; U/ml, units per millilitre.

Notes

a. Downgraded by 2 levels because trial was at high risk of bias due to concerns about the randomisation process, blinding of participants and study personnel,
b. Downgraded by 2 levels because 95% CI crosses 2 MIDs for this outcome.
c. MID for HbA1c is 0.5%. (5.5 mmol/L). MIDs, calculated as 0.5 median SD of the comparison group, for the following continuous outcomes are: Fasting plasma glucose (short term): +/- 1.44; BMI z-score: +/- 0.33.
d. Downgraded by 1 level because 95% CI crosses 1 MID for this outcome.

Table 12: Full GRADE table for SGLT2 inhibitor vs Placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**SGLT2 inhibitor**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Glycated haemoglobin % - short-term change score (≤26 weeks) - Overall												
2	randomised trials	serious[a]	not serious	serious[b]	serious[c,d]	none	91	86	-	MD **0.81 lower** (1.34 lower to 0.28 lower)	⨁◯◯◯ Very low	CRITICAL
Glycated haemoglobin % - short-term change score (≤26 weeks) - Dapagliflozin 10 mg												
1	randomised trials	serious[e]	not serious	serious[f]	serious[c,d]	none	39	33	-	MD **0.75 lower** (1.65 lower to 0.15 higher)	⨁◯◯◯ Very low	CRITICAL
Glycated haemoglobin % - short-term change score (≤26 weeks) - Empagliflozin pooled												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**SGLT2 inhibitor**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	not serious	not serious	not serious	serious[c,d]	none	52	53	-	MD **0.84 mmol/mol lower** (1.49 lower to 0.19 lower)	⊕⊕⊕◯ Moderate	CRITICAL
Participants with HbA1c<6.5% - short term (≤26 weeks) - Empagliflozin pooled												
1	randomised trials	not serious	not serious	not serious	serious[c,d]	none	11/52 (21.2%)	5/53 (9.4%)	**RR 2.24** (0.84 to 6.01)	**117 more per 1,000** (from 15 fewer to 473 more)	⊕⊕⊕◯ Moderate	CRITICAL
Participants with HbA1c<7% - short term (≤26 weeks) - Overall												
2	randomised trials	serious[a]	not serious	serious[b]	very serious[d,g]	none	29/91 (31.9%)	22/86 (25.6%)	**RR 1.25** (0.78 to 1.99)	**64 more per 1,000** (from 56 fewer to 253 more)	⊕◯◯◯ Very low	CRITICAL
Participants with HbA1c<7% - short term (≤26 weeks) - Dapagliflozin 10 mg												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**SGLT2 inhibitor**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious[e]	not serious	serious[f]	very serious[d,g]	none	11/39 (28.2%)	9/33 (27.3%)	**RR 1.03** (0.49 to 2.19)	**8 more per 1,000** (from 139 fewer to 325 more)	⨁◯◯◯ Very low	CRITICAL
Participants with HbA1c<7% - short term (≤26 weeks) - Empagliflozin pooled												
1	randomised trials	not serious	not serious	not serious	very serious[d,g]	none	18/52 (34.6%)	13/53 (24.5%)	**RR 1.41** (0.77 to 2.58)	**101 more per 1,000** (from 56 fewer to 388 more)	⨁⨁◯◯ Low	CRITICAL
Fasting plasma glucose mmol/L - short-term change score (≤26 weeks) - Overall												
2	randomised trials	serious[a]	not serious	serious[b]	not serious[d]	none	87	86	-	MD **1.5 lower** (2.52 lower to 0.48 lower)	⨁⨁◯◯ Low	CRITICAL
Fasting plasma glucose mmol/L - short-term change score (≤26 weeks) - Dapagliflozin 10 mg												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**SGLT2 inhibitor**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious[e]	not serious	serious[f]	not serious[d]	none	39	33	-	MD **0.79 lower** (2.41 lower to 0.85 higher)	⊕⊕◯◯ Low	CRITICAL
Fasting plasma glucose mmol/L - short-term change score (≤26 weeks) - Empagliflozin pooled												
1	randomised trials	not serious	not serious	not serious	not serious[d]	none	48	53	-	MD **1.95 lower** (3.25 lower to 0.48 lower)	⊕⊕⊕⊕ High	CRITICAL
BMI z-score - short term (≤26 weeks) - Dapagflozin 10 mg												
1	randomised trials	serious[e]	not serious	serious[f]	serious[c,d]	none	39	33	-	MD **0.03 higher** (0.08 lower to 0.14 higher)	⊕◯◯◯ Very low	CRITICAL
Weight (kg) - short-term change score (≤26 weeks) - Empagliflozin pooled (follow-up: 26 weeks; assessed with: Kg)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**SGLT2 inhibitor**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	not serious	not serious	serious[h]	not serious[d]	none	52	52	-	MD **0.75 lower** (2.68 lower to 1.18 higher)	⊕⊕⊕◯ Moderate	CRITICAL
Participants needing rescue medication in form of insulin - short term (≤26 weeks) - Overall												
2	randomised trials	serious[a]	not serious	serious[b]	very serious[d,g]	none	7/91 (7.7%)	9/86 (10.5%)	**RR 0.75** (0.29 to 1.91)	**26 fewer per 1,000** (from 74 fewer to 95 more)	⊕◯◯◯ Very low	CRITICAL
Participants needing rescue medication in form of insulin - short term (≤26 weeks) - Dapagliflozin 10 mg												
1	randomised trials	serious[e]	not serious	serious[f]	very serious[d,g]	none	2/39 (5.1%)	3/33 (9.1%)	**RR 0.56** (0.10 to 3.18)	**40 fewer per 1,000** (from 82 fewer to 198 more)	⊕◯◯◯ Very low	CRITICAL
Participants needing rescue medication in form of insulin - short term (≤26 weeks) - Empagliflozin pooled												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**SGLT2 inhibitor**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	not serious	not serious	not serious	very serious[d,g]	none	5/52 (9.6%)	6/53 (11.3%)	**RR 0.85** (0.28 to 2.61)	**17 fewer per 1,000** (from 82 fewer to 182 more)	⊕⊕◯◯ Low	CRITICAL
Serious adverse events - short term (≤26 weeks) - Overall												
2	randomised trials	serious[a]	not serious	serious[b]	very serious[d,g]	none	2/91 (2.2%)	4/86 (4.7%)	**RR 0.46** (0.09 to 2.46)	**25 fewer per 1,000** (from 42 fewer to 68 more)	⊕◯◯◯ Very low	IMPORTANT
Serious adverse events - short term (≤26 weeks) - Dapagliflozin 10 mg												
1	randomised trials	serious[e]	not serious	serious[f]	very serious[d,g]	none	1/39 (2.6%)	2/33 (6.1%)	**RR 0.42** (0.04 to 4.46)	**35 fewer per 1,000** (from 58 fewer to 210 more)	⊕◯◯◯ Very low	IMPORTANT
Serious adverse events - short term (≤26 weeks) - Empagliflozin pooled												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**SGLT2 inhibitor**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	not serious	not serious	not serious	very serious[d,g]	none	1/52 (1.9%)	2/53 (3.8%)	**RR 0.51** (0.05 to 5.45)	**18 fewer per 1,000** (from 36 fewer to 168 more)	⊕⊕◯◯ Low	IMPORTANT
Diabetic ketoacidosis/Hyperosmolar Hyperglycaemic State - short term (≤26 weeks) - Empagliflozin pooled												
1	randomised trials	not serious	not serious	not serious	very serious[d,g]	none	0/52 (0.0%)	1/53 (1.9%)	**RR 0.34** (0.01 to 8.15)	**12 fewer per 1,000** (from 19 fewer to 135 more)	⊕⊕◯◯ Low	IMPORTANT
Severe hypoglycaemic episode - short term (≤26 weeks) - Dapagliflozin 10 mg												
1	randomised trials	serious[e]	not serious	not serious	very serious[d,g]	none	2/39 (5.1%)	1/33 (3.0%)	**RR 1.69** (0.16 to 17.84)	**21 more per 1,000** (from 25 fewer to 510 more)	⊕◯◯◯ Very low	IMPORTANT
Pancreatitis - short term (≤26 weeks) - Empagliflozin pooled												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**SGLT2 inhibitor**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	not serious	not serious	not serious	very serious[d,g]	none	0/52 (0.0%)	1/53 (1.9%)	**RR 0.34** (0.01 to 8.15)	**12 fewer per 1,000** (from 19 fewer to 135 more)	⊕⊕◯◯ Low	IMPORTANT
Other gastrointestinal symptoms: Nausea - short term (≤26 weeks) - Overall												
2	randomised trials	not serious	not serious	not serious	very serious[d,g]	none	6/91 (6.6%)	3/86 (3.5%)	**RR 1.78** (0.49 to 6.48)	**27 more per 1,000** (from 18 fewer to 191 more)	⊕⊕◯◯ Low	IMPORTANT
Other gastrointestinal symptoms: Nausea - short term (≤26 weeks) - Dapgliflozin 10 mg												
1	randomised trials	serious[e]	not serious	serious[f]	very serious[d,g]	none	3/39 (7.7%)	0/33 (0.0%)	**RR 5.95** (0.32 to 111.17)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ Very low	IMPORTANT
Other gastrointestinal symptoms: Nausea - short term (≤26 weeks) - Empagliflozin pooled												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**SGLT2 inhibitor**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	not serious	not serious	not serious	very serious[d,g]	none	3/52 (5.8%)	3/53 (5.7%)	**RR 1.02** (0.22 to 4.82)	**1 more per 1,000** (from 44 fewer to 216 more)	⊕⊕◯◯ Low	IMPORTANT
Other gastrointestinal symptoms: Vomiting - short term (≤26 weeks) - Overall												
2	randomised trials	not serious	not serious	not serious	very serious[d,g]	none	5/91 (5.5%)	2/86 (2.3%)	**RR 2.11** (0.48 to 9.30)	**26 more per 1,000** (from 12 fewer to 193 more)	⊕⊕◯◯ Low	IMPORTANT
Other gastrointestinal symptoms: Vomiting - short term (≤26 weeks) -Dapgliflozin 10 mg												
1	randomised trials	serious[e]	not serious	serious[f]	very serious[d,g]	none	2/39 (5.1%)	0/33 (0.0%)	**RR 4.25** (0.21 to 85.51)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ Very low	IMPORTANT
Other gastrointestinal symptoms: Vomiting - short term (≤26 weeks) - Empagliflozin pooled												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**SGLT2 inhibitor**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	not serious	not serious	not serious	very serious[d,g]	none	3/52 (5.8%)	2/53 (3.8%)	**RR 1.53** (0.27 to 8.78)	**20 more per 1,000** (from 28 fewer to 294 more)	⊕⊕◯◯ Low	IMPORTANT
Other gastrointestinal symptoms: Diarrhoea - short term (≤26 weeks) - Overall												
2	randomised trials	serious[a]	not serious	serious[b]	very serious[d,g]	none	4/91 (4.4%)	7/86 (8.1%)	**RR 0.54** (0.16 to 1.81)	**37 fewer per 1,000** (from 68 fewer to 66 more)	⊕◯◯◯ Very low	IMPORTANT
Other gastrointestinal symptoms: Diarrhoea - short term (≤26 weeks) - Dapgliflozin 10 mg												
1	randomised trials	serious[e]	not serious	serious[f]	very serious[d,g]	none	2/39 (5.1%)	2/33 (6.1%)	**RR 0.85** (0.13 to 5.68)	**9 fewer per 1,000** (from 53 fewer to 284 more)	⊕◯◯◯ Very low	IMPORTANT
Other gastrointestinal symptoms: Diarrhoea - short term (≤26 weeks) - Empagliflozin pooled												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**SGLT2 inhibitor**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	not serious	not serious	not serious	very serious[d,g]	none	2/52 (3.8%)	5/53 (9.4%)	**RR 0.41** (0.08 to 2.01)	**56 fewer per 1,000** (from 87 fewer to 95 more)	⊕⊕◯◯ Low	IMPORTANT
Other gastrointestinal symptoms: Abdominal discomfort - short term (≤26 weeks) - Empagliflozin pooled												
1	randomised trials	not serious	not serious	not serious	very serious[d,g]	none	3/52 (5.8%)	4/53 (7.5%)	**RR 0.76** (0.18 to 3.25)	**18 fewer per 1,000** (from 62 fewer to 170 more)	⊕⊕◯◯ Low	IMPORTANT

Unless otherwise stated, continuous outcomes with MD<0 and dichotomous outcomes with RR<1 favour intervention.

Abbreviations: BMI, body mass index; DPP-4, dipeptidyl peptidase-4; FDC, fixed-dose combination; FPG, fasting plasma glucose; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; IU/mL, international units per millilitre; mg, milligram; mmol/L, millimoles per litre; ng/mL, nanograms per millilitre; U/ml, units per millilitre; SGLT2, Sodium-glucose co-transporter-2; T2DM, Type 2 diabetes mellitus.

Notes
a. Downgraded by 1 level because one trial was at moderate risk of bias with some concerns about the randomisation process (differences between groups for 5 baseline characteristics) and missing data (~20% at end of trial).
b. Downgraded by 1 level because 26% of participants in one trial were young adults (aged 18-24 years).
c. Downgraded 1 level because 95% CI crosses 1 MID for this outcome.
d. MIDs for dichotomous outcomes are 0.8 and 1.25. MID for HbA1c %: +/- 0.5%. MIDs, calculated as 0.5 median SD of the comparison group, for the following outcomes are: Fasting plasma glucose (short term) - overall: +/-3.39; Fasting plasma glucose (short term) - Dapagliflozin 10 mg: +/-3.47 ; Fasting plasma glucose (short term) - Empagliflozin pooled: +/-3.28; BMI z-score: +/-0.12; Weight (kg) (short term) - Empagliflozin pooled: +/-4.96.
e. Downgraded by 1 level because trial was at moderate risk of bias with some concerns about the randomisation process (differences between groups for 5 baseline characteristics) and missing data (~20% at end of trial).

f. Downgraded by 1 level because 26% of participants in the trial were young adults (aged 18-24 years).
g. Downgraded by 2 levels because 95% CI crosses 2 MIDs for this outcome.
h. Downgraded by 1 level because BMI z-score was not reported in trial so weight used as proxy outcome.

Unless otherwise stated, continuous outcomes with MD<0 and dichotomous outcomes with RR<1 favour intervention.

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; mmol/L, millimoles per litre; N/A, not applicable; SGLT2, Sodium-glucose co-transporter-2.

Notes: 1. Downgraded by 1 level because trial was at moderate risk of bias with some concerns about the randomisation process (differences between groups for 5 baseline characteristics) and missing data (~20% at end of trial); 2. Downgraded by 1 level because 26% of participants in the trial were young adults (aged 18-24 years); 3. Downgraded 1 level because 95% CI crosses 1 MID for this outcome; 4. MID for HbA1c %: +/- 0.5%. MID for HbA1c %: +/- 0.5%. MID for HbA1c %: +/- 0.5%; MIDs, calculated as 0.5 median SD of the comparison group, for the following outcomes are: Fasting plasma glucose (short term): +/- 2.72; BMI z-score: +/-0.12; 5. Downgraded 2 levels because 95% CI crosses 2 default MIDs for relative risk outcomes.

Table 13: DPP-4 inhibitor (Linagliptin) vs Placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**DPP-4 inhibitor**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Glycated haemoglobin % - short-term change score (≤26 weeks) - Linagliptin 5mg (follow-up: 26 weeks; assessed with: HbA1c blood test)												
1	randomised trials	not serious	not serious	not serious	serious[a,b]	none	52	53	-	MD **0.34 lower** (0.98 lower to 0.3 higher)	⊕⊕⊕◯ Moderate	CRITICAL
Participants with HbA1c<6.5% - Linagliptin 5 mg (follow-up: 26 weeks; assessed with: HbA1c test)												
1	randomised trials	not serious	not serious	not serious	very serious[c]	none	8/52 (15.4%)	5/53 (9.4%)	**RR 1.63** (0.57 to 4.66)	**59 more per 1,000** (from 41 fewer to 345 more)	⊕⊕◯◯ Low	CRITICAL
Participants with HbA1c<7% - Linagliptin 5 mg (follow-up: 26 weeks; assessed with: HbA1c test)												
1	randomised trials	not serious	not serious	not serious	very serious[c]	none	14/52 (26.9%)	13/53 (24.5%)	**RR 1.10** (0.57 to 2.10)	**25 more per 1,000** (from 105	⊕⊕◯◯ Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DPP-4 inhibitor	Placebo	Relative (95% CI)	Absolute (95% CI)		
										fewer to 270 more)		
Fasting plasma glucose mmol/L - short-term change score (≤26 weeks) - Linagliptin 5 mg (follow-up: 26 weeks; assessed with: FPG blood test)												
1	randomised trials	not serious	not serious	not serious	not serious[b]	none	51	52	-	MD **0.3 lower** (1.58 lower to 0.98 higher)	⊕⊕⊕⊕ High	CRITICAL
Weight (kg) - short-term change score - Linagliptin 5mg												
1	randomised trials	not serious	not serious	serious[d]	not serious[b]	none	50	52	-	MD **1.46 higher** (0.48 lower to 3.4 higher)	⊕⊕⊕◯ Moderate	CRITICAL
Participants needing rescue medication in form of insulin - short term (≤26 weeks) - Linagliptin 5 mg (follow-up: 26 weeks)												
1	randomised trials	not serious	not serious	not serious	very serious[c]	none	4/52 (7.7%)	6/53 (11.3%)	**RR 0.68** (0.20 to 2.27)	**36 fewer per 1,000** (from 91 fewer to	⊕⊕◯◯ Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**DPP-4 inhibitor**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
										144 more)		
Diabetic ketoacidosis/Hyperosmolar Hyperglycaemic State - short term (≤26 weeks) - Linagliptin 5 mg (follow-up: 26 weeks)												
1	randomised trials	not serious	not serious	not serious	very serious[c]	none	0/52 (0.0%)	1/53 (1.9%)	**RR 0.34** (0.01 to 8.15)	**12 fewer per 1,000** (from 19 fewer to 135 more)	⊕⊕◯◯ Low	IMPORTANT
Serious adverse events - short term (≤26 weeks) - Linagliptin 5 mg (follow-up: 26 weeks)												
1	randomised trials	not serious	not serious	not serious	very serious[c]	none	1/52 (1.9%)	1/53 (1.9%)	**RR 1.02** (0.07 to 15.87)	**0 fewer per 1,000** (from 18 fewer to 281 more)	⊕⊕◯◯ Low	IMPORTANT
Pancreatitis - short term (≤26 weeks) - Linagliptin 5 mg (follow-up: 26 weeks)												
1	randomised trials	not serious	not serious	not serious	very serious[c]	none	0/52 (0.0%)	1/53 (1.9%)	**RR 0.34** (0.01 to 8.15)	**12 fewer per 1,000** (from 19 fewer to	⊕⊕◯◯ Low	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**DPP-4 inhibitor**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
										135 more)		
Other gastrointestinal symptoms - short term (≤26 weeks) - Nausea (follow-up: 26 weeks; assessed with: Participant reported)												
1	randomised trials	not serious	not serious	not serious	very serious[c]	none	3/52 (5.8%)	3/53 (5.7%)	**RR 1.02** (0.22 to 4.82)	**1 more per 1,000** (from 44 fewer to 216 more)	⊕⊕◯◯ Low	IMPORTANT
Other gastrointestinal symptoms - short term (≤26 weeks) - Vomiting (follow-up: 26 weeks; assessed with: Participant reported)												
1	randomised trials	not serious	not serious	not serious	very serious[c]	none	5/52 (9.6%)	2/53 (3.8%)	**RR 2.55** (0.52 to 12.55)	**58 more per 1,000** (from 18 fewer to 436 more)	⊕⊕◯◯ Low	IMPORTANT
Other gastrointestinal symptoms - short term (≤26 weeks) - Diarrhoea (follow-up: 26 weeks; assessed with: Participant reported)												
1	randomised trials	not serious	not serious	not serious	very serious[c]	none	3/52 (5.8%)	5/53 (9.4%)	**RR 0.61** (0.15 to 2.43)	**37 fewer per 1,000** (from 80 fewer to	⊕⊕◯◯ Low	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**DPP-4 inhibitor**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
										135 more)		
Other gastrointestinal symptoms - short term (≤26 weeks) - Abdominal discomfort (follow-up: 26 weeks; assessed with: Participant reported)												
1	randomised trials	not serious	not serious	not serious	very serious[c]	none	4/52 (7.7%)	4/53 (7.5%)	**RR 1.02** (0.27 to 3.86)	**2 more per 1,000** (from 55 fewer to 216 more)	⊕⊕◯◯ Low	IMPORTANT

Unless otherwise stated, continuous outcomes with MD<0 and dichotomous outcomes with RR<1 favour intervention.

Abbreviations: BMI, body mass index; DPP-4, dipeptidyl peptidase-4; FDC, fixed-dose combination; FPG, fasting plasma glucose; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; IU/mL, international units per millilitre; mg, milligram; mmol/L, millimoles per litre; ng/mL, nanograms per millilitre; U/ml, units per millilitre; SGLT2, Sodium-glucose co-transporter-2; T2DM, Type 2 diabetes mellitus.

Notes
a. 95% CI crosses 1 MID for this outcome.
b. Minimally important difference (MID) for the following outcome is: HbA1c%, +/-0.5%. MID, calculated as 0.5 times the SD of the control group, for the following outcome is: Fasting plasma glucose, +/-3.28; Weight (kg): +/-4.94.
c. 95% CI crosses two default MIDs for dichotomous outcomes (0.8 and 1.25).
d. Downgraded 1 level because this is proxy outcome as BMI z- score was not reported in trial.

Table 14: Full GRADE table for DPP-4 inhibitor (Sitagliptin) + Metformin vs Metformin

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**DPP-4 inhibitor/Metformin FDC**	**Metformin**	**Relative (95% CI)**	**Absolute (95% CI)**		
Glycated haemoglobin % - Short-term post-intervention score (≤26 weeks) (follow-up: 20 weeks; assessed with: HbA1c blood test)												
1	randomised trials	serious[a]	not serious	not serious	serious[b,c]	none	107	113	-	MD **0.2 lower** (0.57 lower to 0.17 higher)	⊕⊕◯◯ Low	CRITICAL
Glycated haemoglobin % - Long-term post-intervention score (>26 weeks) (follow-up: 54 weeks; assessed with: HbA1c blood test)												
1	randomised trials	serious[a]	not serious	not serious	serious[b,c]	none	70	77	-	MD **0.3 higher** (0.43 lower to 1.03 higher)	⊕⊕◯◯ Low	CRITICAL
Participants with HbA1c<7% - Short term (≤26 weeks) (follow-up: 20 weeks; assessed with: HbA1c blood test)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**DPP-4 inhibitor/Metformin FDC**	**Metformin**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	46/107 (43.0%)	35/113 (31.0%)	**RR 1.39** (0.98 to 1.97)	**121 more per 1,000** (from 6 fewer to 300 more)	⊕⊕◯◯ Low	CRITICAL
Participants with HbA1c<7% - Long term (>26 weeks) (follow-up: 54 weeks; assessed with: HbA1c blood test)												
1	randomised trials	serious[a]	not serious	not serious	very serious[d]	none	22/70 (31.4%)	21/77 (27.3%)	**RR 1.15** (0.70 to 1.91)	**41 more per 1,000** (from 82 fewer to 248 more)	⊕◯◯◯ Very low	CRITICAL
Fasting plasma glucose mmol/L - Short-term post-intervention score (≤26 weeks) (follow-up: 20 weeks; assessed with: FPG blood test)												
1	randomised trials	serious[a]	not serious	not serious	serious[b,c]	none	107	113	-	MD **0.82 lower** (1.66 lower to 0.02 higher)	⊕⊕◯◯ Low	CRITICAL
Fasting plasma glucose mmol/L - Short-term post-intervention score (>26 weeks) (follow-up: 54 weeks; assessed with: FPG blood test)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**DPP-4 inhibitor/Metformin FDC**	**Metformin**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious[a]	not serious	not serious	serious[b,c]	none	70	77	-	MD **0.34 higher** (0.75 lower to 1.43 higher)	⊕⊕◯◯ Low	CRITICAL
BMI kg/m2 - Short-term change score (≤26 weeks) (follow-up: 20 weeks)												
1	randomised trials	serious[a]	not serious	serious[e]	not serious[c]	none	107	113	-	MD **0.2 lower** (0.64 lower to 0.24 higher)	⊕⊕◯◯ Low	CRITICAL
BMI kg/m2 - Long-term change score (>26 weeks) (follow-up: 54 weeks)												
1	randomised trials	serious[a]	not serious	serious[e]	not serious[c]	none	70	77	-	MD **0.3 higher** (0.48 lower to 1.08 higher)	⊕⊕◯◯ Low	CRITICAL
Participants needing rescue medication in form of insulin - short term (≤26 weeks) - Short term (≤26 weeks) (follow-up: 20 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**DPP-4 inhibitor/Metformin FDC**	**Metformin**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious[a]	not serious	not serious	not serious	none	4/107 (3.7%)	19/113 (16.8%)	**RR 0.22** (0.08 to 0.63)	**131 fewer per 1,000** (from 155 fewer to 62 fewer)	⊕⊕⊕◯ Moderate	CRITICAL
Participants needing rescue medication in form of insulin - short term (≤26 weeks) - Long term (>26 weeks) (follow-up: 54 weeks)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	19/70 (27.1%)	30/77 (39.0%)	**RR 0.70** (0.43 to 1.12)	**117 fewer per 1,000** (from 222 fewer to 47 more)	⊕⊕◯◯ Low	CRITICAL
Serious adverse events - Short term (≤26 weeks) (follow-up: 20 weeks)												
1	randomised trials	serious[a]	not serious	not serious	very serious[d]	none	5/107 (4.7%)	3/113 (2.7%)	**RR 1.76** (0.43 to 7.19)	**20 more per 1,000** (from 15 fewer to 164 more)	⊕◯◯◯ Very low	IMPORTANT
Serious adverse events - Long term (>26 weeks) (follow-up: 54 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**DPP-4 inhibitor/Metformin FDC**	**Metformin**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious[a]	not serious	not serious	very serious[d]	none	5/70 (7.1%)	4/77 (5.2%)	**RR 1.38** (0.38 to 4.92)	**20 more per 1,000** (from 32 fewer to 204 more)	⊕◯◯◯ Very low	IMPORTANT
Severe hypoglycaemic episode - Short term (≤26 weeks) (follow-up: 20 weeks)												
1	randomised trials	serious[a]	not serious	not serious	very serious[d]	none	3/107 (2.8%)	4/113 (3.5%)	**RR 0.79** (0.18 to 3.46)	**7 fewer per 1,000** (from 29 fewer to 87 more)	⊕◯◯◯ Very low	IMPORTANT
Severe hypoglycaemic episode - Long term (>26 weeks) (follow-up: 54 weeks)												
1	randomised trials	serious[a]	not serious	not serious	very serious[d]	none	2/70 (2.9%)	2/77 (2.6%)	**RR 1.10** (0.16 to 7.60)	**3 more per 1,000** (from 22 fewer to 171 more)	⊕◯◯◯ Very low	IMPORTANT
Other gastrointestinal symptoms - short term (≤26 weeks) - Nausea (follow-up: 20 weeks; assessed with: Participant reported)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**DPP-4 inhibitor/Metformin FDC**	**Metformin**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious[a]	not serious	not serious	very serious[d]	none	5/107 (4.7%)	7/113 (6.2%)	**RR 0.75** (0.25 to 2.30)	**15 fewer per 1,000** (from 46 fewer to 81 more)	⊕◯◯◯ Very low	IMPORTANT
Other gastrointestinal symptoms - short term (≤26 weeks) - Vomiting (follow-up: 20 weeks; assessed with: Participant reported)												
1	randomised trials	serious[a]	not serious	not serious	very serious[d]	none	4/107 (3.7%)	4/113 (3.5%)	**RR 1.06** (0.27 to 4.12)	**2 more per 1,000** (from 26 fewer to 110 more)	⊕◯◯◯ Very low	IMPORTANT
Other gastrointestinal symptoms - short term (≤26 weeks) - Diarrhoea (follow-up: 20 weeks; assessed with: Participant reported)												
1	randomised trials	serious[a]	not serious	not serious	very serious[d]	none	9/107 (8.4%)	5/113 (4.4%)	**RR 1.90** (0.66 to 5.49)	**40 more per 1,000** (from 15 fewer to 199 more)	⊕◯◯◯ Very low	IMPORTANT
Other gastrointestinal symptoms - short term (≤26 weeks) - Abdominal discomfort (follow-up: 20 weeks; assessed with: Participant reported)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**DPP-4 inhibitor/Metformin FDC**	**Metformin**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	5/107 (4.7%)	14/113 (12.4%)	**RR 0.38** (0.14 to 1.01)	**77 fewer per 1,000** (from 107 fewer to 1 more)	⊕⊕◯◯ Low	IMPORTANT
Other gastrointestinal symptoms - long term (≤26 weeks) - Nausea (follow-up: 54 weeks; assessed with: Participant reported)												
1	randomised trials	serious[a]	not serious	not serious	very serious[d]	none	5/70 (7.1%)	3/77 (3.9%)	**RR 1.83** (0.45 to 7.39)	**32 more per 1,000** (from 21 fewer to 249 more)	⊕◯◯◯ Very low	IMPORTANT
Other gastrointestinal symptoms - long term (≤26 weeks) - Vomiting (follow-up: 54 weeks; assessed with: Participant reported)												
1	randomised trials	serious[a]	not serious	not serious	very serious[d]	none	2/70 (2.9%)	2/77 (2.6%)	**RR 1.10** (0.16 to 7.60)	**3 more per 1,000** (from 22 fewer to 171 more)	⊕◯◯◯ Very low	IMPORTANT
Other gastrointestinal symptoms - long term (>26 weeks) - Diarrhoea (follow-up: 54 weeks; assessed with: Participant reported)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**DPP-4 inhibitor/Metformin FDC**	**Metformin**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious[a]	not serious	not serious	very serious[d]	none	4/70 (5.7%)	6/77 (7.8%)	**RR 0.73** (0.22 to 2.49)	**21 fewer per 1,000** (from 61 fewer to 116 more)	⨁◯◯◯ Very low	IMPORTANT
Other gastrointestinal symptoms - long term (>26 weeks) - Abdominal discomfort (follow-up: 54 weeks; assessed with: Participant reported)												
1	randomised trials	serious[a]	not serious	not serious	very serious[d]	none	5/70 (7.1%)	7/77 (9.1%)	**RR 0.79** (0.26 to 2.36)	**19 fewer per 1,000** (from 67 fewer to 124 more)	⨁◯◯◯ Very low	IMPORTANT

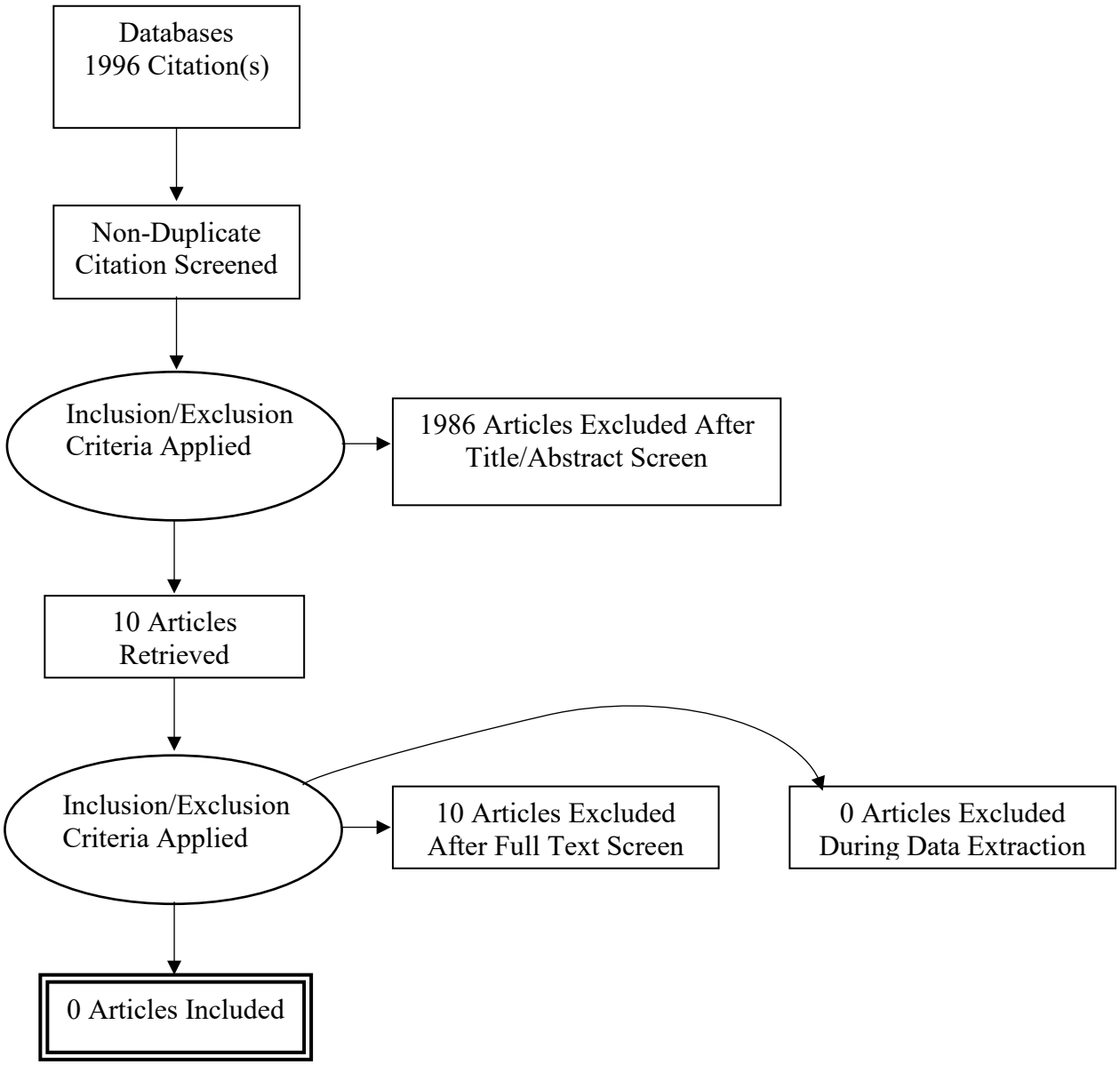
Unless otherwise stated, continuous outcomes with MD<0 and dichotomous outcomes with RR<1 favour intervention.

Abbreviations: BMI, body mass index; DPP-4, dipeptidyl peptidase-4; FDC, fixed-dose combination; FPG, fasting plasma glucose; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; IU/mL, international units per millilitre; mg, milligram; mmol/L, millimoles per litre; ng/mL, nanograms per millilitre; U/ml, units per millilitre; SGLT2, Sodium-glucose co-transporter-2; T2DM, Type 2 diabetes mellitus.

Notes
a. Downgraded by 1 level because trial was at moderate risk of bias with some concerns about the randomisation process (no information provided) and missing data (~34% at end of trial).
b. Downgraded by 1 level because 95% CI crosses 1 MID for this outcome.
c. MID for HbA1c %: +/- 0.5%. MIDs, calculated as 0.5 median SD of the comparison group, for the following outcomes are: Fasting plasma glucose (short term): +/- 1.61; Fasting plasma glucose (long term): +/- 1.40; BMI kg/m2 (short term): +/- 0.85; BMI kg/m2 (long term): +/-1.25.

d. Downgraded by 2 levels because 95% CI crosses 2 MIDs for this outcome.
e. Downgraded by 1 level because reported outcome was not adjusted for age and sex as specified in protocol.

Appendix G – Economic evidence study selection



Appendix H – Economic evidence tables

No economic evidence was found for this review question.

Appendix I – Health economic model

No original health economic modelling was done for this review question.

Appendix J – Excluded studies

Effectiveness evidence

Table 15: Excluded studies - Effectiveness evidence

Study	Reason for exclusion
Bensignor, Megan O, Bomberg, Eric M, Bramante, Carolyn T et al. (2021) Effect of liraglutide treatment on body mass index and weight parameters in children and adolescents with type 2 diabetes: Post hoc analysis of the ellipse trial. Pediatric obesity 16(8): e12778	- Secondary publication of an included study that does not provide any additional relevant information
Chadda, Karan R; Cheng, Tuck Seng; Ong, Ken K (2021) GLP-1 agonists for obesity and type 2 diabetes in children: Systematic review and meta-analysis. Obesity reviews : an official journal of the International Association for the Study of Obesity 22(6): e13177	- Systematic review used as source of primary studies
Currie, Brooke M, Howell, Timothy A, Matza, Louis S et al. (2021) A Review of Interventional Trials in Youth-Onset Type 2 Diabetes: Challenges and Opportunities. Diabetes therapy : research, treatment and education of diabetes and related disorders 12(11): 2827-2856	- No additional articles identified
Hannon, Tamara S, Edelstein, Sharon L, Arslanian, Silva A et al. (2020) Withdrawal of medications leads to worsening of OGTT parameters in youth with impaired glucose tolerance or recently-diagnosed type 2 diabetes. Pediatric diabetes 21(8): 1437-1446	- Less than 70% of participants had Type 2 Diabetes
Jean-Baptiste, E, Larco, P, von Oettingen, J et al. (2021) Efficacy of a New Protocol of Premixed 70/30 Human Insulin in Haitian Youth with Diabetes. Diabetes Therapy 12(9): 2545-2556	- Less than 70% of participants had Type 2 Diabetes
Middleton, Timothy L, Constantino, Maria I, McGill, Margaret et al. (2022) Improving beta-cell secretory function and glycaemia in young-onset type 2 diabetes: A pilot, 12-month, randomized trial of a novel, continuous glucose monitor-guided, rapid treatment intensification strategy incorporating empagliflozin and liraglutide. Diabetes, obesity & metabolism 24(4): 747-751	- Less than 50% participants are children and young people *Adult participants (18-40 yrs)*
RISE, Consortium (2018) Impact of Insulin and Metformin Versus Metformin Alone on beta-Cell Function in Youth With Impaired Glucose Tolerance or Recently Diagnosed Type 2 Diabetes. Diabetes care 41(8): 1717-1725	- Less than 70% of participants had Type 2 Diabetes

Study	Reason for exclusion
TODAY Study, Group (2021) Postintervention Effects of Varying Treatment Arms on Glycemic Failure and beta-Cell Function in the TODAY Trial. Diabetes care 44(1): 75-80	- Drug not available in the UK
Wu, Sijia, He, Yina, Wu, Yutong et al. (2022) Comparative efficacy and safety of glucose-lowering drugs in children and adolescents with type 2 diabetes: A systematic review and network meta-analysis. Frontiers in endocrinology 13: 897776	- Systematic review used as source of primary studies
Xu, H-Y and Si, H-Y (2014) Clinical effect of subcutaneous insulin injection combined with metformin for type 2 diabetes mellitus in children. World chinese journal of digestology 22(10): 1479-1483	- Study not reported in English

Economic evidence

Table 16: Excluded studies - Economic evidence

Study	Reason for exclusion
Bagepally, Bhavani Shankara, Chaikledkaew, Usa, Gurav, Yogesh Krishnarao et al. (2020) Glucagon-like peptide 1 agonists for treatment of patients with type 2 diabetes who fail metformin monotherapy: systematic review and meta-analysis of economic evaluation studies. BMJ open diabetes research & care 8(1)	- Systematic review used as source of primary studies *All papers included had a population with a mean age from 50.9 to 64.7 years.*
Bagepally, Bhavani Shankara, Gurav, Yogesh Krishnarao, Anothaisintawee, Thunyarat et al. (2019) Cost Utility of Sodium-Glucose Cotransporter 2 Inhibitors in the Treatment of Metformin Monotherapy Failed Type 2 Diabetes Patients: A Systematic Review and Meta-Analysis. Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research 22(12): 1458-1469	- Systematic review used as source of primary studies *All references checked but the populations were only in adults*
Degli Esposti, Luca, Saragoni, Stefania, Buda, Stefano et al. (2014) Clinical outcomes and health care costs combining metformin with sitagliptin or sulphonylureas or thiazolidinediones in uncontrolled type 2	- Does not contain a population of children with diabetes *The population is only adults*

Study	Reason for exclusion
diabetes patients. ClinicoEconomics and outcomes research: CEOR 6: 463-72	
Guzauskas, Gregory F, Rind, David M, Fazioli, Katherine et al. (2021) Cost-effectiveness of oral semaglutide added to current antihyperglycemic treatment for type 2 diabetes. Journal of managed care & specialty pharmacy 27(4): 455-468	- Does not contain a population of children with diabetes *Only adults were modelled*
Hasanzad, Mandana, Sarhangi, Negar, Nikfar, Shekoufeh et al. (2020) A narrative review of current trends in liraglutide: insights into the unmet needs in management of type 2 diabetes and obesity. Journal of diabetes and metabolic disorders 19(2): 1863-1872	- Not a relevant study design *Not a cost effectiveness study*
Kalirai, Samaneh, Duan, Ran, Liu, Dongju et al. (2017) Economic Impact of Treatment Duration and Persistence with Basal Insulin in Previously Insulin-Naive Users. Journal of managed care & specialty pharmacy 23(3): 327-336	- Does not contain a population of children with diabetes *Study based on a population with the intervention with an average age 51.8 years and the comparator 50.1 years*
McEwan, Phil, Morgan, Angharad R, Boyce, Rebecca et al. (2021) The cost-effectiveness of dapagliflozin in treating high-risk patients with type 2 diabetes mellitus: An economic evaluation using data from the DECLARE-TIMI 58 trial. Diabetes, obesity & metabolism 23(4): 1020-1029	- Does not contain a population of children with diabetes *Study contains cohort with starting age of 63.80 years*
Songer, Thomas J, Haymond, Morey W, Glazner, Judith E et al. (2019) Healthcare and associated costs related to type 2 diabetes in youth and adolescence: the TODAY clinical trial experience. Pediatric diabetes 20(6): 702-711	- Not a relevant study design *Costing study, does not look into effectiveness*
Tzanetakos, Charalampos, Tentolouris, Nicholas, Kourlaba, Georgia et al. (2016) Cost-Effectiveness of Dapagliflozin as Add-On to Metformin for the Treatment of Type 2 Diabetes Mellitus in Greece. Clinical drug investigation 36(8): 649-59	- Does not contain a population of children with diabetes *Modelling adults only, starting age 58.4 years or 57.52 years.*

Study	Reason for exclusion
Valentine, W J, Curtis, B H, Pollock, R F et al. (2015) Is the current standard of care leading to cost-effective outcomes for patients with type 2 diabetes requiring insulin? A long-term health economic analysis for the UK. Diabetes research and clinical practice 109(1): 95-103	- Does not contain a population of children with diabetes *Population had a mean age of 65.6 years*

Appendix K– Research recommendations – full details

K1.1 Research recommendation 1

In children and young people with type 2 diabetes, what is the effectiveness of glucose-lowering agents used to manage blood glucose levels in adults with type 2 diabetes? **(New 2023)**

K1.1.1 Why this is important

In contrast to the paediatric population, there is a plethora of glucose-lowering agents used to manage blood glucose levels in adults with type 2 diabetes. Increasing the number of potential treatments will allow clinicians to offer more flexibility when treating type 2 diabetes in the paediatric population and reduce the need to change treatments when transitioning to adult diabetes services.

K1.1.2 Rationale for research recommendation 1

Table 17: Rationale for research recommendation 1

Importance to 'patients' or the population	There are very few glucose-lowering agents that have been shown to effectively manage blood glucose levels for children and young people with type 2 diabetes. Increasing treatment options will enable better and more individualised treatment.
Relevance to NICE guidance	New 2023 review of glucose-lowering agents to manage blood glucose levels in combination with, or as an alternative to, metformin in children and young people with type 2 diabetes identified few trials conducted since 2014.
Relevance to the NHS	Increasing treatment options will enable better, more individualised treatment.
National priorities	High
Current evidence base	The current review shows that since 2014, there has only been 1 RCT examining potential second-line alternatives to metformin and 6 RCTs examining potential agents that can be combined with metformin.
Equality considerations	None known

K1.1.3 Modified PICO table

Table 18: Modified PICO table for research recommendation 1

Population	Children and young people with type 2 diabetes
Intervention	Glucose-lowering agent(s) used to manage blood glucose levels in adults with type 2 diabetes
Comparator	Placebo or a different glucose-lowering agent(s) used to manage blood glucose levels in adults with type 2 diabetes
Outcome	Glycaemic control (HbA1c %, glucose levels); side effects
Study design	Randomised controlled trial
Timeframe	Long term
Additional information	None

K1.2 Research recommendation 2

In children and young people with type 2 diabetes, what is the effectiveness of weekly treatment with glucose-lowering agents for managing blood glucose levels compared to daily treatment? **(New 2023)**

K1.2.1 Why this is important

Children and young people with type 2 diabetes can sometimes find it difficult to fully adhere with their prescribed medication and having daily injections can be onerous and may lead to stigma (for example, at school).

K1.2.2 Rationale for research recommendation

Table 19: Rationale for research recommendation 2

Importance to 'patients' or the population	Daily subcutaneous injections can be onerous for children and young people with type 2 diabetes. Establishing whether weekly injections is more effective could reduce their treatment burden.
Relevance to NICE guidance	Daily and weekly injections of GLP-1 receptor agonists have been considered in this review.
Relevance to the NHS	Medium
National priorities	Low
Current evidence base	There is little head-to-head RCT evidence comparing the administration of weekly vs daily glucose-lowering agents for improving glycaemic control.
Equality considerations	None known

K1.2.3 Modified PICO table

Table 20: Modified PICO table for research recommendation 2

Population	Children and young people with type 2 diabetes
Intervention	Weekly subcutaneous injection
Comparator	Daily subcutaneous injection
Outcome	Glycaemic control (HbA1c %, glucose levels); side effects
Study design	Randomised controlled trial
Timeframe	Long term

Additional information	None

Appendix L – Methods

Review protocols

A review protocol was developed with the guideline committee to outline the inclusion and exclusion criteria used to select studies for each evidence review. Where possible, review protocols were prospectively registered in the PROSPERO register of systematic reviews.

Searching for evidence

Evidence was searched for each review question using the methods specified in the 2018 NICE guidelines manual.

Selecting studies for inclusion

All references identified by the literature searches and from other sources (for example, from published systematic reviews) were uploaded into EPPI reviewer software version 5 and de-duplicated. Titles and abstracts were assessed for possible inclusion using the criteria specified in the review protocol. 10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.

The full text of potentially eligible studies was retrieved and assessed according to the criteria specified in the review protocol. A standardised form was used to extract data from included studies.

Data synthesis for intervention studies

Where possible, meta-analyses were conducted to combine the results of quantitative studies for each outcome. Network meta-analyses was considered in situations where there were at least 3 treatment alternatives. When there were 2 treatment alternatives, pairwise meta-analysis was used to compare interventions.

Appraising the quality of the evidence

RCTs were quality assessed using the Cochrane Risk of Bias Tool. Evidence on each outcome for each individual study was classified into one of the following groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.

- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the following areas: population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Clinical decision thresholds and assessing imprecision

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference (MID) thresholds relevant to this guideline that might aid the committee in identifying clinical decision thresholds for the purpose of GRADE. Identified MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline. In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus clinical decision threshold could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one treatment is not meaningfully worse than another) required a clinical decision threshold to be defined to act as a non-inferiority margin.

Clinical decision thresholds used in the guideline are given below in Table 22.

Table 21: Clinical decision thresholds used in this evidence review

Outcome	Minimally Important Difference threshold (Source)
HbA1c (% or mmol/l)	0.5% or 5.5 mmol/ mol (Little 2013)
Glucose level: Time in range (%)	5% change in time in range (Battelino 2019)
PEDS-QL	Hilliard 2013
PEDS-QL generic youth	4.72 score

Outcome	Minimally Important Difference threshold (Source)
PEDS-QL generic parent	4.88 score
PEDS-QL diabetes youth	5.27 score
PEDSQL diabetes parent	4.54 score

For continuous outcomes expressed as a mean difference where no other MID was available, an MID of 0.5 of the median standard deviations of the comparison group arms will be used (Norman et al. 2003). For relative risks where no other MID is available, default MIDS of 0.8 and 1.25 will be used. When decisions are made in situations where MIDs are not available, the 'Evidence to Recommendations' section of this review will make explicit the committee's view of the expected clinical importance and relevance of the findings. In particular, this will include consideration of whether the effect of a treatment (which may be felt across multiple independent outcome domains) is likely to be clinically meaningful as a whole.