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HEALTH TECHNOLOGY BRIEFING FEBRUARY 2021

Tirzepatide for treating type 2 diabetes mellitus

NIHRIO ID	28192	**NICE ID**	10338
Developer/Company	Eli Lilly and Company	**UKPS ID**	655617

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Tirzepatide is in clinical development for the treatment of type 2 diabetes mellitus (T2DM). T2DM is a lifelong condition that develops when the body becomes resistant to, or does not produce enough insulin – a hormone produced in the pancreas. Insulin is needed to control the amount of sugar in the blood. A lack of insulin, or resistance to insulin in T2DM patients causes blood sugar levels too become too high. If blood sugar remains high over a long period of time this can result in serious complications. For some T2DM patients, existing anti-diabetic medications are ineffective at controlling blood sugar levels. Therefore, there is a need to develop new treatment options that are more effective in reducing blood sugar levels in T2DM patients.

Tirzepatide is a new type of drug that is administered by subcutaneous injection and acts on two proteins known as the gastric inhibitory peptide (GIP) and glucagon-like peptide-1 (GLP-1) and results in more insulin being released from the pancreas. Tirzepatide has the potential to improve blood sugar levels and increase weight loss compared to current treatment options. If licenced, tirzepatide will offer an additional treatment option for patients with T2DM.

PROPOSED INDICATION

Adults with T2DM.[a]

TECHNOLOGY

DESCRIPTION

Tirzepatide (LY3298176) is a dual receptor agonist that acts at the receptors of both the GIP and GLP-1, two primary hormones which are secreted from the intestine to stimulate insulin secretion in response to ingested nutrients.[1,2]

Tirzepatide is currently in clinical development for the treatment of T2DM. In the phase III clinical trials (SURPASS J-combo, NCT03861039; SURPASS-1, NCT03954834; SURPASS-2, NCT03987919; SURPASS-3, NCT03882970; SURPASS-4, NCT03730662; SURPASS-5, NCT04039503) participants are given either 5mg, 10 mg or 15mg of tirzepatide, delivered subcutaneously, once a week.[3-6]

INNOVATION AND/OR ADVANTAGES

There are a number of different medications available to people with diabetes. However, not all medications are suitable to all T2DM patients.[7] Some patients may still have inadequately controlled blood sugar despite taking anti-diabetic medication or experience side effects such as hypoglycaemia.[8]

Tirzepatide is a novel dual GIP and GLP-1 receptor agonist that has showed significantly greater glucose control and weight loss compared to the selective GLP-1 receptor agonist dulaglutide in a phase 2 study.[9]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Tirzepatide does not currently have Marketing Authorisation in the EU/UK for any indication.

Tirzepatide is also in phase II or III clinical development for the treatment of obesity and non-alcoholic steatohepatitis (NASH).[10]

PATIENT GROUP

DISEASE BACKGROUND

T2DM is the most common type of diabetes, accounting for around 90% of all diabetes diagnoses.[11] T2DM develops when the body becomes resistant to insulin which is a hormone secreted by the pancreas into the bloodstream that helps glucose enter cells from the blood.[12,13]
The pancreas can compensate for this insulin resistance for a while by producing more insulin, but at some point it can no longer keep up and then blood glucose levels rise

[a] Information provided by Eli Lilly and Company Limited on UK PharmaScan

(hyperglycaemia).[12,14] Being overweight is the main risk factor for T2DM. However, other risk factors such as storing fat mainly in the abdomen, having high blood pressure, being physically inactive, having a family history of T2DM, being of South Asian, African-Caribbean or Black African descent, increasing age, developing gestational diabetes and polycystic ovarian syndrome also increase the risk of developing T2D.[13,15]

Symptoms of T2DM include urinating more than usual, particularly at night, feeling thirsty all the time, feeling tired, itching around the penis or vagina, repeatedly getting thrush and cuts or wounds that take longer to heal and blurred vision.[16]

If diabetes is not well controlled, the resultant hyperglycaemia over a long period of time can damage the blood vessels and result in the chronic complications associated with diabetes.[17,18] These complications include; diabetic retinopathy, foot ulcers, heart disease, stroke, nephropathy, neuropathy, gum disease, sexual problems such as urinary tract infections in women and erectile dysfunction in men.[18,19] Low blood glucose (hypoglycaemia) can also be a complication of T2DM if patients do not eat enough carbohydrate whilst taking insulin or medications called sulfonylureas. Hypoglycaemia is more likely to develop if patients miss a meal, take other medications such as beta-blockers, drink too much alcohol or do more physical activity than usual.[19]

CLINICAL NEED AND BURDEN OF DISEASE

In 2018-19 there were 3,319,266 people in England who were currently diagnosed with diabetes. Based on the estimation that 90% of these diagnoses would be T2DM this equates to around 3 million people living with T2DM in England.[11,20] In the UK, around 700 people a day are diagnosed with diabetes. By 2025, it is estimated that 5 million people will have diabetes in the UK.[21]

In England, in 2019-20 there were 50,654 finished consultant episodes (FCE) for T2DM (ICD-10 code E11), resulting in 28,516 admissions, 3,168 day cases and 212,379 FCE bed days.[22] Diabetes care is estimated to account for at least 5% of UK healthcare and up to 10% of NHS expenditure.[11]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The primary aim of treating T2DM is to control blood glucose levels to reduce the risk of developing complications later in life. An individualised approach to diabetes care should be adopted which is tailored to the needs and circumstances of adults with T2DM. All patients should be offered a structured education programme to help them develop the attitude, belief, knowledge and skills to self-manage their diabetes.[11,23] Some patients with T2DM can manage their condition with lifestyle measures such as eating a balanced, low-sugar diet and taking regular exercise. However, other patients may require medication to manage their blood glucose levels.[24]

Taking a haemoglobin A1c (HbA1c) test is the main way of assessing diabetes management as it shows the average blood glucose over the previous three months. The target HbA1c for adults with T2DM should be 48 mmol/mol (6.5%) or lower if managed by lifestyle and diet alone or lifestyle and diet combined with a single drug not associated with hypoglycaemia. The target HbA1c for adults with T2DM should be 53 mmol/mol (7%) or lower if managed by

a drug associated with hypoglycaemia. However, this target may be relaxed if intensive management is not appropriate for a the patient.[25]

CURRENT TREATMENT OPTIONS

NICE currently recommends the following treatment options for patients with T2DM:[8,26]

Patients who can tolerate metformin:
Standard-release metformin is the first drug treatment offered to adults with T2DM whose blood glucose is not adequately controlled with lifestyle interventions alone.

First intensification therapy involves dual therapy with metformin and one of the following:
- dipeptidyl peptidase-4 (DPP-4) inhibitor (linagliptin, saxagliptin, sitapliptin or vildagliptin)
- pioglitazone
- sulfonylurea (glibenclamide, gliclazide, glimepiride, glipizide, tolbutamide)
- sodium glucose co-transporter 2 (SGLT2) inhibitor (canagliflozin, dapagliflozin or empagliflozin)

Second intensification therapy involves starting insulin based treatment or triplet therapy with metformin and one of the following:
- DPP-4 inhibitor and a sulfonylurea
- pioglitazone and a sulfonylurea
- sulfonylurea and a SGLT2 inhibitor
- pioglitazone and a SGLT2 inhibitor (canagliflozin or empagliflozin only)

If triple therapy with metformin and two other oral drugs is not effective, not tolerated or contra-indicated then a GLP-1 receptor agonist may be prescribed as part of a triple combination regimen with metformin and a sulfonylurea.

Patients who cannot tolerate metformin:
If metformin is contraindicated or not tolerated, initial drug treatment to be offered is one of the following:
- a DPP-4 inhibitor
- pioglitazone
- sulfonylurea
- SGLT2 inhibitor
- repaglinide

First intensification if metformin is contraindicated or not tolerated involves combination therapy with one of the following:
- a DPP-4 inhibitor and pioglitazone
- a DPP-4 inhibitor and a sulfonylurea
- pioglitazone and a sulfonylurea

If dual therapy does not provide adequate glucose control, insulin-based treatment should be considered
- isophane insulin
- insulin determir
- insulin glargine

PLACE OF TECHNOLOGY

If licensed, tirzepatide will offer an additional treatment option for patients with T2DM.[3-6,27,28]

CLINICAL TRIAL INFORMATION

Trial	**SURPASS-1**, NCT03954834; A randomized, Double-blind, Placebo-Controlled Trial Comparing the Efficacy and Safety of Three Tirzepatide Doses Versus Placebo in Patients With Type 2 Diabetes, Inadequately Controlled With Diet and Exercise Alone **Phase III** – Completed **Locations:** United States and other countries **Study completion date:** October 2020
Trial design	Randomised, Parallel assignment, Double-blind, Placebo-controlled
Population	N=478; adults aged 18 years and older; diagnosed with T2DM; naïve to diabetes injectable therapies and have not used any oral antihyperglycaeimic medications during the 2 months preceding screening; HbA1c between ≥7% and ≤9.5%
Intervention(s)	Arm 1: 5mg tirzepatide once a week (subcutaneous injection) Arm 2: 10mg tirzepatide once a week (subcutaneous injection) Arm 3: 15mg tirzepatide once a week (subcutaneous injection)
Comparator(s)	Placebo administered once a week (subcutaneous injection)
Outcome(s)	Primary outcome measure: • Change from baseline HbA1c [Time Frame: Baseline, Week 40] Please see trial record for full list of outcome measures
Results (efficacy)	In the SURPASS-1 trial, once-daily treatment with tirzepatide 15mg over 40 weeks resulted in an A1c reduction of 2.07% from baseline and led to reductions in body weight by 11% from baseline. Approximately 51.7% of patients in the tirzepatide arm achieved an A1C of less than 5.7%, a level observed in people without diabetes. These primary and key secondary endpoints of changes in A1c and body weight reductions, respectively, were significantly greater than in the placebo group.[29]
Results (safety)	The drug's overall safety profile was similar to the well-established GLP-1 receptor agonist class. The most common adverse events reported in the patients were gastrointestinal side effects. Treatment discontinuation rates due to adverse events were less than 7% in each tirzepatide treatment arm.[29]

Trial	**SURPASS-2,** NCT03987919**;** A Phase 3, Randomized, Open-Label Trial Comparing Efficacy and Safety of Tirzepatide

	Versus Semaglutide Once Weekly as Add-on Therapy to Metformin in Patients With Type 2 Diabetes **Phase III** – Active, not recruiting **Locations:** UK, USA, Canada and other countries **Estimated primary completion date:** January 2021
Trial design	Randomised, Parallel assignment, Open-label
Population	N=1881; adults aged 18 years and older; diagnosed with T2DM; HbA1c between ≥7.0% and ≤10.5%; be on stable treatment with unchanged dose of metformin >1500 mg/day for at least 3 months prior to screening
Intervention(s)	Arm 1: 5mg tirzepatide once a week (subcutaneous injection) Arm 2: 10mg tirzepatide once a week (subcutaneous injection) Arm 3: 15mg tirzepatide once a week (subcutaneous injection)
Comparator(s)	Semaglutide administered once a week (subcutaneous injection)
Outcome(s)	Primary outcome measure: • Change from baseline in HbA1c (10mg and 15mg) [Time Frame: Baseline, Week 40] See trial record for full list of outcome measures
Results (efficacy)	-
Results (safety)	-

Trial	**SURPASS-3,** NCT03882970**;** EudraCT 2018-003422-84**;** A Randomized, Phase 3, Open-Label Trial Comparing the Effect of LY3298176 Versus Titrated Insulin Degludec on Glycaemic Control in Patients With Type 2 Dibetes **Phase III** – Completed **Locations**: 7 EU countries, USA and other countries **Study completion date**: December 2020
Trial design	Randomised, Open-label, Parallel assignment
Population	N=1444; diagnosed with T2DM; have a HbA1c between ≥7.0% and ≤10.5%; be on stable treatment with unchanged dose of metformin or metformin plus an SGLT-2 inhibitor for at least 2 months before screening
Intervention(s)	Arm 1: 5mg tirzepatide once a week (subcutaneous injection) Arm 2: 10mg tirzepatide once a week (subcutaneous injection) Arm 3: 15mg tirzepatide once a week (subcutaneous injection)
Comparator(s)	Insulin degludec administered once a day (subcutaneous injection)
Outcome(s)	Primary outcome measure • Change from baseline in HbA1c) (10mg and 15mg) [Time Frame: Baseline, Week 52] See trial record for full list of outcome measures
Results (efficacy)	-
Results (safety)	-

Trial	**SURPASS-4,** NCT03730662, EudraCT 2018-002618-11; Efficacy and Safety of LY3298176 Once Weekly Versus Insulin Glargine in Patients With Type 2 Diabetes and Increased Cardiovascular Risk **Phase III** – Active, not recruiting **Locations:** 5 EU countries, USA, Canada and other countries **Estimated primary completion date:** May 2021
Trial design	Randomised, Parallel Assignment, Open-label
Population	N=1878; diagnosed with T2DM; HbA1c between ≥7.5% and ≤10.5%; be on stable treatment with unchanged dose of at least 1 and no more than 3 types of oral antihyperglycemic drugs, which can include metformin, SGLT-2 inhibitors, and/or sulfonylureas for at least months before screening; have increased risk for cardiovascular events
Intervention(s)	Arm 1: 5mg tirzepatide once a week (subcutaneous injection) Arm 2: 10mg tirzepatide once a week (subcutaneous injection) Arm 3: 15mg tirzepatide once a week (subcutaneous injection)
Comparator(s)	Insulin glargine administered once a day (subcutaneous injection)
Outcome(s)	Primary outcome measure: • Change from baseline in haemoglobin A1c (HbA1c) (10mg and 15mg) [Time Frame: Baseline, Week 52] See trial record for full list of outcome measures
Results (efficacy)	-
Results (safety)	-

Trial	**SURPASS-5;** NCT04039503**;** EudraCT 2019-00860-99**;** Randomized, Phase 3, Double-blind Trial Comparing the Effect of the Addition of Tirzepatide Versus Placebo in Patients With Type 2 Diabetes Inadequately Controlled On Insulin Glargine With or Without Metformin **Phase III** – Active, not recruiting **Locations:** 5 EU countries, USA and other countries **Primary completion date:** December 2020
Trial design	Randomised, Parallel assignment, double blinded
Population	N=472; adults aged 18 years and older; diagnosed with T2D; have been treated with insulin glargine (U100), once daily with or without metformin ≥3 months prior to screening visit; HbA1c between ≥7.0% and ≤10.5%
Intervention(s)	Arm 1: 5mg tirzepatide once a week (subcutaneous injection) Arm 2: 10mg tirzepatide once a week (subcutaneous injection) Arm 3: 15 mg tirzepatide once a week (subcutaneous injection)
Comparator(s)	Placebo administered once a week (subcutaneous injection)
Outcome(s)	Primary outcome measure • Change from baseline in HbA1c (10mg and 15mg) [Time Frame: Baseline, Week 40] See trial record for full list of outcome measures
Results (efficacy)	-
Results (safety)	-

Trial	**SURPASS-COVT,** NCT04255433, 2019-002735-28; The Effect of Tirzepatide Versus Dulaglutide on Major Adverse Cardiovascular Events in Patients With Type 2 Diabetes **Phase III** – Recruiting Locations: 15 EU countries (incl UK), US, Canada and other countries **Estimated primary completion date**: October 2024
Trial design	Randomised, Parallel Assignment, Double Masked
Population	N=12500; diagnosis of type 2 diabetes; confirmed atherosclerotic cardiovascular disease; HbA1c ≥7.0% and <10.5%; BMI ≥25 kg/m^2
Intervention(s)	Tirzepatide administered subcutaneously once a week
Comparator(s)	Dulaglutide administered subcutaneously once a week
Outcome(s)	Primary outcome measure • Time to first occurrence of death from cardiovascular causes, myocardial infarction or stroke (MACE-3) [Time Frame: randomization up to study completion (approximate maximum 54 months)] See trial record for full list of outcome measures
Results (efficacy)	-
Results (safety)	-

Trial	**SURPASS J-combo;** NCT03861039**;** A Phase 3, Long-Term Safety Study of Tirzepatide in Combination With Monotherapy of Oral Antihyperglycemic Medications in Patients With T2DM **Phase III** – Active, not recruiting **Location:** Japan **Estimated primary completion date:** February 2021
Trial design	Randomised, Parallel assignment, Open-label,
Population	N=441; adults aged 20 years and older; diagnosed with T2DM based on the World Health Organization (WHO) classification; have HbA1c ≥7.0% and <11.0%; have been taking sulfonylureas, biguanides, thiazolidinedione, alpha-glucosidase inhibitor, glinides, or sodium-glucose cotransporter type 2 inhibitor monotherapy for at least months before screening and have been on the following Dose for at least 8 weeks before screening
Intervention(s)	Arm 1: 5mg tirzepatide once a week (subcutaneous injection) Arm 2: 10mg tirzepatide once a week (subcutaneous injection) Arm 3: 15mg tirzepatide once a week (subcutaneous injection)
Comparator(s)	No Comparator
Outcome(s)	Primary outcome measure: • Number of participants with one or more serious adverse events considered by the investigator to be related to study drug administration [Time Frame: Baseline through Week 52] See trial record for full list of outcome measures

Trial	**SURPASS-6;** NCT04537923, 2020-000284-23; A Randomized, Phase 3, Open-label Trial Comparing the Effect of the Addition of Tirzepatide Once Weekly Versus Insulin Lispro (U100) Three Times Daily in Participants With Type 2 Diabetes Inadequately Controlled on Insulin Glargine (U100) With or Without Metformin **Phase III** – Recruiting **Locations:** 9 EU countries (not incl UK), USA and other countries Estimated primary completion date: July 2022
Trial design	Randomised, Parallel assignment, Open-label,
Population	N=441; diagnosed with T2DM; HbA1c between ≥7.5% and ≤11.0%; have been treated for at least 90 days prior to day of screening with once or twice daily basal insulin with or without stable dose of metformin; be of stable weight (± 5%) for at least 90 days; BMI ≥23 kg/m^2 and ≤45 kg/m^2 at screening
Intervention(s)	Arm 1: 5mg tirzepatide once a week with U100 insulin glargine (subcutaneous injection) Arm 2: 10mg tirzepatide once a week with U100 (subcutaneous injection) Arm 3: 15mg tirzepatide once a week with U100 (subcutaneous injection)
Comparator(s)	U100 insulin lispro administered three times a day with U100 insulin glargine (subcutaneous injection)
Outcome(s)	Primary outcome measure: • Change from baseline in HbA1c (pooled dosed) [Time Frame: baseline, week 52] See trial record for full list of outcome measures

ESTIMATED COST

The estimated cost of tirzepatide is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Semaglutide for treating type 2 diabetes (ID1450). Expected publication date to be confirmed.
- NICE technology appraisal in development. Dulaglutide for treating type 2 diabetes (ID1451). Expected publication date to be confirmed.
- NICE technology appraisal in development. Sotagliflozin for treating type 2 diabetes. (ID1657). Expected publication date to be confirmed.
- NICE technology appraisal. Ertugliflozin with metformin and a dipeptidyl peptidase-4 inhibitor for treating type 2 diabetes (TA583). June 2019

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NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Insulin-Resistant Diabetes Services (All Ages). A03/S(HSS)/b.
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OTHER GUIDANCE

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ADDITIONAL INFORMATION

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