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Tirzepatide for Type 2 Diabetes Mellitus

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Key Messages

- Horizon Scan reports provide brief summaries of information regarding new and emerging health technologies; Heath Technology Update articles typically focus on a single device or intervention. These technologies are identified through the CADTH Horizon Scanning Service as topics of potential interest to health care decision-makers in Canada. This Horizon Scan summarizes the available information regarding an emerging technology, tirzepatide, for the treatment of hyperglycemia in adults with type 2 diabetes.
- Type 2 diabetes (T2D) is a metabolic disease where blood glucose concentrations cannot be maintained at a normal level (hyperglycemia). Several antihyperglycemia drugs are currently available for the treatment of T2D including metformin, insulin secretagogues (meglitinides, sulfonylureas), dipeptidyl peptidase-4 (DPP4) inhibitors, sodium glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like polypeptide-1 (GLP-1) receptor agonists, thiazolidinediones, alpha-glucosidase inhibitors, and slow/fast-acting insulin analogues. Despite the number of drugs currently available to mitigate hyperglycemia, a significant unmet need for new therapeutics still exists.
- Tirzepatide (LY3298176; Eli Lilly Inc.) is a first in class dual glucagon-like polypeptide-1 (GLP-1) receptor and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist currently under development to treat hyperglycemia and obesity in individuals with T2D.
- To date, phase III clinical trials have been completed and several other trials are in progress to determine the efficacy of tirzepatide to reduce hyperglycemia (SURPASS studies) and obesity (SURMOUNT-2 study) in adults with T2D.
- This Horizon Scan bulletin focuses on the glycemic effect of tirzepatide in T2D. In summary, tirzepatide demonstrates efficacy in reducing mean glycated hemoglobin (A1C) compared to placebo, semaglutide, insulin degludec, and insulin glargine. Studies investigating the possible effect of tirzepatide on cardiovascular outcomes are currently ongoing.

Methods

These bulletins are not systematic reviews and do not involve critical appraisal or include a detailed summary of study findings. Rather, they present an overview of the technology and available evidence. They are not intended to provide recommendations for or against a particular technology.

Literature Search Strategy

A limited literature search was conducted by an information specialist on key resources including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. Clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, WHO's International Clinical Trials Registry Platform (ICTRP) search portal, Health Canada's Clinical Trials Database, and the European Union Clinical Trials Register. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was tirzepatide. No filters were applied to limit the retrieval by study type.

Where possible, retrieval was limited to the human population. The search was not restricted by language or date of publication.

Study Selection

One author screened the literature search results and reviewed the full text of all potentially relevant studies. Studies were considered for inclusion if the intervention was tirzepatide, the clinical trials were in phase III of development, and the condition was T2D. Conference abstracts and grey literature were included when they provided additional information to that available in the published studies.

Peer Review

A draft version of this bulletin was reviewed by a clinical expert. The sponsor was also given the opportunity to comment on an earlier draft.

Background

Diabetes is a metabolic disease characterized by an inability to produce and efficiently utilize insulin. As a result, patients with diabetes have difficulty regulating the concentration of glucose in their blood and experience hyperglycemia (high blood glucose). Diabetes is primarily classified as type 1, type 2, or gestational diabetes. Approximately 3 million Canadians (8.1%) are living with diabetes, representing 1 in 10 Canadian adults.[1] Every year approximately 201,000 Canadians are newly diagnosed with diabetes.[2] It is estimated that 90% of Canadians with diabetes have type 2 diabetes (T2D).[1] T2D is multifaceted and can be caused by several factors, including but not limited to poor diet, obesity, physical inactivity, genetics, and environmental factors.

Diagnosis and management of T2D are determined by repetitive measurements of blood glucose concentrations or the percentage of A1C and symptoms of hyperglycemia. A fasting plasma glucose measurement of at least 7 mmol/L, a plasma glucose of at least 11.1 mmol/L 2 hours following a glucose tolerance test, a random plasma glucose measurement of at least 11.1 mmol/L, or a A1C of at least 6.5% are diagnostic criteria of T2D.[3] If left untreated, T2D can lead to various hyperglycemia-associated complications such as neuropathy, nephropathy, retinopathy, and cardiovascular disease.[4] Consequently, patients with T2D are at a heightened risk for major adverse cardiovascular events (MACE) and may have decreased life expectancy.[4]

Based on Diabetes Canada clinical practice guidelines, metformin is the first-line treatment option for T2D due to its cost-effectiveness and safety profile.[5] Several next-line antidiabetic drugs are available based on individual patient characteristics such as the risk or presence of heart failure, atherosclerotic cardiovascular disease, or kidney disease.[6] These drugs include insulin secretagogues (meglitinides, sulfonylureas), dipeptidyl peptidase-4 (DPP4) inhibitors, sodium glucose cotransporter 2 (SGLT2) inhibitors, GLP-1 receptor agonists, thiazolidinediones, alpha-glucosidase inhibitors, and slow/fast-acting insulin analogues.[7]

Common side effects of antihyperglycemia medications include nausea (metformin, GLP-1 receptor agonists), weight gain (meglitinides, sulfonylureas, thiazolidinediones, insulin), and hypoglycemia risk (meglitinides, sulfonylureas, insulin).[5] GLP-1 receptor agonists and

SGLT2 inhibitors have been associated with weight loss and lower risks of hypoglycemia.[6] Due to early concerns that certain antidiabetic drugs may increase cardiovascular disease, and the inherent cardiovascular risk associated with T2D, both the Federal Drug Agency (FDA) of the US and Health Canada issued guidance on the development of new antidiabetic drugs emphasizing long-term cardiovascular safety.[8,9] Cardiovascular outcome trials have shown that newer glucose lowering medications, such as GLP-1 receptor agonist and SGLT2 inhibitors, may have advantages on not only glycemic control, but complications of T2D including weight gain and cardiovascular and renal diseases.[10]

Glycemic control is fundamental to diabetes management.[11] However, even with available antihyperglycemia medications, Canadian's with T2D are not achieving glycemic targets.[12]

The Technology

Tirzepatide (LY3298176; Eli Lilly Inc.) is a dual GLP-1 receptor and GIP receptor agonist under development to improve blood glucose concentrations, obesity, and heart failure with preserved ejection fraction. This Horizon Scan bulletin focuses on the effect of tirzepatide on glycemia in T2D. GLP-1 signalling reduces blood glucose concentrations by increasing glucose-dependent insulin release, slowing gastric emptying, and inhibiting glucagon release.[6] Similarly, GIP signalling enhances meal-time insulin secretion to reduce blood glucose.[13] However, the secretion of both incretins is diminished in populations with T2D.[14] GIP receptors are also found in the hypothalamus, which suggests a role of GIP in signalling satiety.[13] The combination of both GLP-1 and GIP receptor agonism has been shown in early clinical trials to improve glycemia and reduce body weight to a greater extent than GLP-1 agonism alone.[15]

Regulatory Status

Tirzepatide is currently under review at the European Medicines Agency (submitted October 28, 2021)[16] and the US FDA (submitted October 27, 2021).[17]

Cost and Administration

Cost information for tirzepatide is currently unavailable. Tirzepatide is administered as a weekly subcutaneous injection. Phase III trials investigated the efficacy of tirzepatide at 5 mg, 10 mg, and 15 mg dosages; however, it is unknown what dosages will receive regulatory approval.

Target Population

Tirzepatide is initially anticipated to be used as a mono or adjunctive therapy to improve glycemic control in patients with T2D.

Current Practice

Diabetes Canada released full clinical practice guidelines for the prevention and management of diabetes in 2018[4] and provided an update on pharmacologic glycemic management of T2D in adults in 2020.[6] Patients with T2D are a heterogenous population, making treatment regimens and glycemic targets (i.e., A1C) for T2D highly individualized and complex.[11] Treatment focuses on limiting hyperglycemia-associated symptoms (metabolic decompensation, ketoacidosis, dehydration, fatigue, etc.) and mitigating long-term complications such as heart, kidney, and vascular diseases.

In adults, if the A1C is lower than or equal to 1.5% above an individual's glycemic target at diagnosis, behavioural interventions are initially emphasized (nutritional guidance, physical activity).[6] If glycemic targets are not reached within 3 months, or A1C is at least 1.5% above their glycemic target, behavioural interventions are supplemented with antihyperglycemia pharmacotherapy.[6] Metformin is the first-line of therapy for T2D when hyperglycemia-related symptoms are not present; however, when hyperglycemia-associated symptoms are present, insulin with or without metformin is recommended.[6] If A1C is 1.5% above an individual's glycemic target at diagnosis, initiating metformin in combination with a second antihyperglycemic agent, such as DPP4 inhibitors, insulin secretagogues (meglitinides, sulfonylureas), thiazolidinediones, SGLT2 inhibitors, or GLP-1 receptor agonists is recommended. Choice of second-line antihyperglycemic medications by health-care providers balance many factors including hyperglycemia, risk of hypoglycemia, body weight, efficacy of antihyperglycemic drugs for reducing blood glucose and limiting diabetes complications, adherence, affordability, side effects, and patient preferences.[6]

In adults with T2D that have established, or risk factors for, atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease, GLP1 receptor agonist and SGLT2 inhibitors are recommended.[6] In addition, insulin treatment may also be initiated in individuals not achieving glycemic targets. Several antihyperglycemia medications are available in combination forms. Throughout the course of T2D treatment, antihyperglycemic drugs are often added, adjusted, and delicately balanced to meet the individual needs of the patient with T2D.

Summary of the Evidence

The literature search identified a total of 10 phase III trials from the SURPASS trial program (Table 1). Five trials are now complete with published full-text articles (SURPASS 1 to 5),[13,18-21] 3 trials are complete but with no available results (SURPASS-J-mono, -J-compo, -AP-combo),[22-24] and 2 trials are ongoing (SURPASS-6, SURPASS-CVOT).[25,26] Trials without data or in progress will be discussed in the Concurrent Developments section. Phase III trials

investigating tirzepatide for additional indications are also briefly discussed in the Concurrent Developments section.

SURPASS-1

The SURPASS-1 study[13,27] was a multi-centre (4 countries, not including Canada) phase III, randomized, double-blind, placebo-controlled trial. Participants were 18 years of age or older with T2D (N = 478), naive to diabetes injectable therapies, had a BMI of at least 23 kg/m^2, and had inadequate glycemic control with diet and exercise alone (A1C 7.0% to 9.5%) at screening. Patients with T1D, history of pancreatitis, retinopathy, diabetic maculopathy, non-proliferative diabetic retinopathy requiring treatment, estimated glomerular filtration rate lower than or equal to 30 mL/min per 1.73 m^2, or have used any oral antihyperglycemia medication for 3 months before screen were not included in the study. Baseline participant characteristics were similar between experimental groups. Across all trial participants the mean age of participants was 54.1 years of age, time since T2D diagnosis was 4.7 years, A1C 7.94%, BMI 31.9 kg/m^2, and 54% of participants had not previously received oral hyperglycemic medications. After a 3-week screening period, participants were randomly assigned (1:1:1:1) to receive subcutaneous injections of tirzepatide (5 mg, 10 mg, or 15 mg) once weekly or placebo for 40 weeks. To reduce gastrointestinal tolerability, tirzepatide dosing was increased at 2.5 mg increments every 4 weeks until the maintenance dose was achieved. The primary outcome measure was the mean change in A1C from baseline at 40 weeks (reported here as efficacy estimand) and participants were monitored an additional 4 weeks to assess safety.

Tirzepatide reduced A1C across all 3 doses from baseline at 40 weeks. Compared to baseline, A1C decreased by a mean of −1.87% (standard error [SE] 0.09) with 5 mg tirzepatide (P < 0.0001), −1.89% (SE 0.10) with 10 mg tirzepatide (P < 0.0001), and −2.07% (SE 0.10) with 15 mg tirzepatide (P < 0.0001), compared to + 0.04% (SE 0.11) with placebo (P = 0.72). A higher proportion of participants receiving tirzepatide reached a target A1C of less than 7.0% (87% to 92% tirzepatide participants versus 19% placebo), a A1C of less than 6.5% (81% to 86% tirzepatide participants versus 10% placebo) or an A1C of less than 5.7% (31% to 52% tirzepatide participants versus 1% placebo).

A total of 11 serious adverse events were identified throughout the trial; 5 (4%) in participants that received 5 mg tirzepatide, 2 (2%) in participants that received 10 mg tirzepatide, 1 (1%) in participants that received 15 mg tirzepatide, versus 3 (3%) with placebo. No deaths were reported in participants that received tirzepatide and the most frequent adverse events were gastrointestinal. Nausea was reported in 14 (12%), 16 (13%), 22 (18%) participants receiving 5, 10, and 15 mg of tirzepatide, respectively, versus 7 (6%) in placebo. Diarrhea was reported in 14 (12%), 17 (14%), 14 (12%) participants receiving 5, 10, and 15 mg of tirzepatide, respectively, versus 9 (8%) in placebo. Hypoglycemia (< 4 mmol/L) was reported in 7 (6%) participants that received 5 mg tirzepatide, in 8 (7%) in participants that received 10 mg of tirzepatide. and in 8 (7%) in participants that received 15 mg of tirzepatide, compared to 1 (1%) in the placebo group. Severe hypoglycemia (< 3 mmol/L) was not reported in any tirzepatide participants.

SURPASS-2

The SURPASS-2 study[19,28] was a multi-centre (8 countries, including Canada) phase III, open-label, randomized controlled trial that compared the efficacy and safety of tirzepatide versus semaglutide, a selective GLP-1 agonist. Participants were 18 years of age or older with T2D (N = 1,878), had inadequate glycemic control with metformin (1,500 mg/day), A1C

Table 1: Characteristics of Completed Phase III Randomized Controlled Trials

Author, year, Name of study, NCT number	Study design, Study duration, Sample size	Population	Intervention	Comparator(s)	Primary outcome(s)
Rosenstock et al. 2021[13] **SURPASS-1** (NCT03954834)	Double-blind, placebo controlled 40 weeks N = 478	T2D (≥ 18 years old) Naive to diabetes injectable therapies ≥ 3 months since taking OAM ≥ 3 months stable body weight A1C 7.0% to 9.5% BMI ≥ 23 kg/m^2	5 mg tirzepatide weekly SC (n = 121) 10 mg tirzepatide weekly SC (n = 121) 15 mg tirzepatide weekly SC (n = 121)	Placebo SC (n = 115)	Mean change in A1C from baseline
Frías et al. 2021[19] **SURPASS-2** (NCT03987919)	Open label 40 weeks N = 1,878	T2D A1C 7.0% to 10.5% ≥ 3 months stable metformin treatment (≥ 1,500 mg/day) ≥ 3 months stable body weight BMI ≥ 25 kg/m^2	5 mg tirzepatide weekly SC (n = 470) 10 mg tirzepatide weekly SC (n = 469) 15 mg tirzepatide weekly SC (n = 470)	Semaglutide weekly SC (n = 469)	Mean change in A1C from baseline
Ludvik et al. 2021[20] **SURPASS-3** (NCT03882970)	Open label 52 weeks N = 1,444	T2D Insulin naive A1C 7.0% to 10.5% ≥ 3 months stable metformin (≥ 1,500 mg/day) or metformin plus SGLT-2 inhibitor treatment ≥ 3 months stable body weight BMI ≥ 25 kg/m^2	5 mg tirzepatide weekly SC (n = 358) 10 mg tirzepatide weekly SC (n = 360) 15 mg tirzepatide weekly SC (n = 359)	Insulin degludec daily SC (n = 360)	Mean change in A1C from baseline

Author, year, Name of study, NCT number	Study design, Study duration, Sample size	Population	Intervention	Comparator(s)	Primary outcome(s)
Del Prato et al. 2021[18] **SURPASS-4** (NCT03730662)	Open label 104 weeks (primary end point 54 weeks) N = 2,002	T2D A1C 7.5% to 10.5% ≥ 1-month stable treatment ≤ 3 oral antihyperglycemic drugs (metformin, SGLT-2 inhibitors, sulfonylureas) and ≥ 3 months stable treatment ≥ 3 months stable body weight BMI ≥ 25 kg/m^2 Increased risk of cardiovascular events	5 mg tirzepatide weekly SC (n = 329) 10 mg tirzepatide weekly SC (n = 328) 15 mg tirzepatide weekly SC (n = 338)	Insulin glargine daily SC (n = 1,000)	Mean change in A1C from baseline
Dahl et al. 2022[21] **SURPASS-5** (NCT04039503)	Double blind 40 weeks N = 475	T2D A1C 7.0% to 10.5% ≥ 3 months treated with insulin glargine (U100) once daily with/without metformin ≥ 3 months stable body weight BMI ≥ 23 kg/m^2	5 mg tirzepatide weekly SC (n = 116) 10 mg tirzepatide weekly SC (n = 119) 15 mg tirzepatide weekly SC (n = 120)	Placebo SC (n = 120)	Mean change in A1C from baseline

A1C = glycated hemoglobin; BMI = body mass index, DPP4 = Dipeptidyl peptidase-4; MACE = major adverse cardiovascular event; OAM = oral antihyperglycemic medication; RCT = randomized controlled trials; SAE = severe adverse event; SGLT-2 = sodium glucose cotransporter; T2D = Type 2 diabetes.

between 7.0% to 10.5%, BMI of at least 25 kg/m^2, and had stable weight (± 5%) the previous 3 months. Patients with T1D, estimated glomerular filtration rate at least 45 mL/min per 1.73 m^2, history of pancreatitis, non-proliferative diabetic retinopathy that required urgent treatment, proliferative diabetic neuropathy, or diabetic maculopathy were not included in the study. The mean age of participants was 56.6 years of age, time since T2D diagnosis was 8.6 years, A1C 8.28%, and a BMI 34.2 kg/m^2. Participants were randomly assigned (1:1:1:1) to receive subcutaneous injections of tirzepatide (5 mg, 10 mg, or 15 mg; doses were double-blind) once weekly or semaglutide (1 mg) for 40 weeks. Tirzepatide dosing was increased at 2.5 mg increments every 4 weeks until the maintenance dose was achieved. Beginning at a dose of 0.25 mg, semaglutide dosing was doubled weekly until 1 mg was reached at week 4. The primary outcome measure was the mean change in A1C from baseline at 40 weeks (reported here as efficacy estimand) and participants were monitored an additional 4 weeks to assess safety.

Compared to baseline, at 40 weeks tirzepatide reduced mean A1C by 2.09% (SEM 0.05) at 5 mg ($P < 0.001$), 2.37% (SEM 0.05) at 10 mg ($P < 0.001$), and 2.46% (SEM 0.05) at 15 mg

(P < 0.001), compared to a 1.86% (SEM 0.05) reduction with semaglutide (P < 0.001). All 3 doses of tirzepatide reduced A1C to a greater extent than semaglutide; estimated treatment differences of −0.15 percentage points for 5 mg tirzepatide (95% confidence interval [CI], −0.28 to −0.03; P = 0.02), −0.39 percentage points for 10 mg tirzepatide (95% CI, −0.51 to −0.26; P < 0.001), −0.45 percentage points for 15 mg tirzepatide (95% CI, −0.57 to −0.32; P < 0.001). A higher proportion of participants receiving tirzepatide reached a target A1C of less than 7.0% (82% to 86% tirzepatide participants versus 79% semaglutide), an A1C less than 6.5% (69% to 80% tirzepatide participants versus 64% semaglutide) or an A1C of less than 5.7% (27% to 46% tirzepatide participants versus 19% semaglutide).

A total of 98 serious adverse events were identified throughout the study, with more occurring in tirzepatide participants than semaglutide; 33 (7%) in participants that received 5 mg tirzepatide, 25 (5.3%) in participants that received 10 mg tirzepatide, 27 (5.7%) in participants that received 15 mg tirzepatide, versus 13 (2.8%) in semaglutide. A total of 13 deaths (0.7%) occurred in the trial population (tirzepatide, n = 4 [0.9%] in each treatment arm and semaglutide, n = 1 [0.2%]). The most frequent reported adverse events were gastrointestinal, including but not limited to nausea (17% to 22% tirzepatide versus 18% semaglutide), diarrhea (13% to 16% tirzepatide versus 12% semaglutide), and vomiting (6% to 10% tirzepatide versus 8% semaglutide). Hypoglycemia (< 3 mmol/L) was reported in 3 (0.6%) participants that received 5 mg tirzepatide, in 1 (0.2%) in participants that received 10 mg of tirzepatide. and in 8 (1.7%) in participants that received 15 mg of tirzepatide, compared to 2 (0.4%) who received semaglutide.

SURPASS-3

The SURPASS-3 study[20,29] was a multi-centre (13 countries, not including Canada) phase III, open-label, randomized controlled trial that compared the efficacy of tirzepatide to insulin degludec, a long-acting basal insulin analogue. Patients were 18 years of age or older with T2D (N = 1,444), insulin naive, had inadequate glycemic control on a stable dose of metformin, with or without SGLT2 inhibitors for at least 3 months before screening. In addition, participants had an A1C between 7.0% to 10.5%, a BMI at least 25 kg/m^2, and stable weight (± 5%) for at least 3 months. Patients with T1D, history of pancreatitis, diabetic retinopathy or maculopathy, and an estimated glomerular filtration rate of lower than or equal to 45 mL/min per 1.73 m^2 were not included in the study. The mean age of participants was 57.4 years of age, time since T2D diagnosis was 8.4 years, A1C 8.17%, and a BMI 33.5 kg/m^2. The majority of participants in the SURPASS-3 study were white (91%). Participants were randomly assigned (1:1:1:1) to receive a subcutaneous injection of tirzepatide (5 mg, 10 mg, or 15 mg) weekly or insulin degludec daily for 52 weeks. Tirzepatide dosing was increased at 2.5 mg increments every 4 weeks until the maintenance dose was achieved. Insulin degludec was administered with a prefilled pen containing 3 mL (U100/mL) daily, titrating weekly starting with 10 U per day. The primary outcome measure was mean change in A1C from baseline at 52 weeks (reported here as efficacy estimand) and participants were monitored an additional 4 weeks to assess safety.

At 52 weeks, compared to baseline, mean A1C decreased by −1.93% (SE 0.05) with 5 mg tirzepatide, −2.20% (SE 0.05) with 10 mg tirzepatide, and −2.37% (SE 0.05) with 15 mg tirzepatide, compared to −1.34% (SE 0.05) with insulin degludec. Estimated treatment differences versus insulin degludec was −0.59 percentage points for 5 mg tirzepatide (95% confidence interval [CI], −0.73 to −0.45; P < 0.0001), −0.86 percentage points for 10 mg tirzepatide (95% CI, −1.00 to −0.72; P < 0.0001), −1.04 percentage points for 15 mg tirzepatide (95% CI, −1.17 to −0.90; P < 0.0001). A higher proportion of participants receiving tirzepatide

reached a target A1C of less than 7.0% (82% to 93% tirzepatide participants versus 61% insulin degludec), an A1C of less than 6.5% (71% to 85% tirzepatide participants versus 44% insulin degludec) or an A1C of less than 5.7% (26% to 48% tirzepatide participants versus 5% insulin degludec).

A total of 97 serious adverse events were identified throughout the study, which were evenly distributed between tirzepatide and insulin degludec treated participants; 29 (8%) in participants that received 5 mg tirzepatide, 20 (6%) in participants that received 10 mg tirzepatide, 26 (7%) in participants that received 15 mg tirzepatide, versus 22 (6%) in insulin degludec. A total of 5 deaths (0.3%) occurred in the trial population and were evenly distributed across participants. The most frequent reported adverse events were gastrointestinal and occurred to a greater extent in tirzepatide treated participants. Gastrointestinal symptoms were primarily nausea (12% to 24% tirzepatide versus 2% insulin degludec), diarrhea (15% to 17% with tirzepatide versus 4% with insulin degludec), decreased appetite (6% to 12% tirzepatide versus 1% insulin degludec), and vomiting (6% to 10% tirzepatide versus 1% insulin degludec). Hypoglycemia (< 3 mmol/L) was reported in 5 (1%) participants that received 5 mg tirzepatide, in 4 (1%) in participants that received 10 mg of tirzepatide. and in 7 (2%) in participants that received 15 mg of tirzepatide, compared to 26 (7%) who received insulin degludec.

SURPASS-4

The SURPASS-4 study[18,30] was a multi-centre (14 countries, including Canada) phase III, open-label, randomized controlled trial that compared the efficacy of tirzepatide to insulin glargine, a long-acting basal insulin analogue. Patients were 18 years of age or older with T2D (N = 2,002), that had inadequate glycemic control with any combination of metformin, sulfonylurea, or SGLT-2 inhibitors. In addition, participants had an A1C between 7.5% to 10.5%, a BMI of at least 25 kg/m^2, stable weight (± 5%) for at least 3 months, and at increased risk of cardiovascular events. Cardiovascular risk was defined as coronary, peripheral arterial, or cerebrovascular disease, or 50 years of age or older with a history of chronic kidney disease (estimated glomerular filtration rate of lower than or equal to 60 mL/min per 1.73 m^2) or history of congestive heart failure. Across trial participants the mean age was 63.6 years of age, mean duration of diabetes was 11.8 years, A1C 8.52%, and a BMI 32.6 kg/m^2. Most trial participants were white (81.5%), with the remaining participants identifying as Asian (3.5%), Native Hawaiian, or other Pacific Islander (0.2%), Black/African American (3.8%), American Indian, or Alaska Native (8.7%), or more than 1 race (2.1%). Participants were randomly assigned (1:1:1:3) to receive a subcutaneous injection of tirzepatide (5 mg, 10 mg, or 15 mg) weekly or insulin glargine daily for 52 weeks. Tirzepatide dosing was increased at 2.5 mg increments every 4 weeks until the maintenance dose was achieved. Insulin glargine was administered with a prefilled pen containing 3 mL (U100/mL) daily, titrating weekly starting with 10 U per day. The primary outcome measure was mean change in A1C from baseline at 52 weeks (reported here as efficacy estimand) and participants were monitored an additional 4 weeks to assess safety.

At 52 weeks, compared to baseline, mean A1C decreased by −2.24% (SE 0.05) with 5 mg tirzepatide, −2.43% (SE 0.05) with 10 mg tirzepatide, and −2.58% (SE 0.05) with 15 mg tirzepatide, compared to −1.44% (SE 0.05) with insulin glargine. Estimated treatment differences versus insulin glargine was −0.80 percentage points for 5 mg tirzepatide (95% confidence interval [CI], −0.92 to −0.68; P < 0.0001), −0.99 percentage points for 10 mg tirzepatide (95% CI, −1.11 to −0.87; P < 0.0001), −1.14 percentage points for 15 mg tirzepatide (95% CI, −1.26 to −1.02; P < 0.0001). A higher proportion of participants receiving tirzepatide

reached a target A1C of less than 7.0% (81% to 91% tirzepatide participants versus 51% insulin glargine), an A1C of less than 6.5% (66% to 81% tirzepatide participants versus 32% insulin glargine) or an A1C of less than 5.7% (23% to 43% tirzepatide participants versus 3% insulin glargine).

A total of 336 serious adverse events were identified throughout the study; 48 (15%) in participants that received 5 mg tirzepatide, 54 (17%) in participants that received 10 mg tirzepatide, 41 (12%) in participants that received 15 mg tirzepatide, versus 193 (19%) in insulin glargine. A total of 60 deaths occurred in trial participants (tirzepatide, n = 25 [3%] and glargine, n = 35 [4%]) and no increased risk of major adverse cardiac events (MACE-4) for pooled tirzepatide versus glargine was identified (hazard ratio [HR 0.74], 95% CI, 0.51 to 1.08). The most frequent reported adverse events were gastrointestinal, including but not limited to nausea (12% to 23% tirzepatide versus 2% insulin glargine), diarrhea (13% to 22% tirzepatide versus 4% insulin glargine), vomiting (5% to 9% tirzepatide versus 2% insulin glargine), and loss of appetite (9% to 11% tirzepatide versus < 1% insulin glargine). Hypoglycemia (< 3 mmol/L) was reported in 29 (9%) participants that received 5 mg tirzepatide, in 20 (6%) in participants that received 10 mg of tirzepatide, and in 27 (8%) in participants that received 15 mg of tirzepatide, compared to 191 (19%) who received insulin glargine.

SURPASS-5

The SURPASS-5 study[21,31,32] was a multi-centre (8 countries, not including Canada) phase III, randomized, double-blind, placebo-controlled trial that compared the efficacy of tirzepatide to placebo in patients with T2D that were already on insulin glargine, with or without metformin. Participants were 18 years of age or older with T2D (N = 475), treated with insulin glargine (U100), once daily with or without metformin for at least 3 months, had a BMI at least 23 kg/m^2, had inadequate glycemic control (A1C 7.0% to 10.5%) at screening, and stable weight (± 5%) for at least 3 months. Participants with pancreatitis, diabetic retinopathy or maculopathy, or an estimated glomerular filtration rate 30 mL/min or less per 1.73m^2 were not included in the study. Across trial participants the mean age was 60.6 years of age, A1C was 8.31%, and a BMI 33.4 kg/m^2. Most trial participants were white (80%), with the remaining participants identifying as Asian (17.9%), Black/African American (1.3%), American Indian or Alaska Native (0.4%), or more than 1 race (0.4%). Participants were randomly assigned (1:1:1:1) to receive a weekly subcutaneous injection of tirzepatide (5 mg, 10 mg, or 15 mg) weekly or placebo for 40 weeks. The primary outcome measure was mean change in A1C from baseline at 40 weeks (reported here as efficacy estimand) and participants were monitored an additional 4 weeks to assess safety.

Compared to baseline, A1C decreased by −2.23% (SE 0.08) with 5 mg tirzepatide, −2.59% (SE 0.08) with 10 mg tirzepatide, and −2.59% (SE 0.08) with 15 mg tirzepatide, compared to −0.93% (SE 0.08) with placebo. Estimated treatment differences versus placebo was −1.30 percentage points for 5 mg tirzepatide (95% confidence interval [CI], −1.52 to −1.07; P < 0.001), −1.66 percentage points for 10 mg tirzepatide (95% CI, −1.88 to −1.43; P < 0.001), −1.65 percentage points for 15 mg tirzepatide (95% CI, −1.88 to −1.43; P < 0.001).A higher proportion of participants receiving tirzepatide reached a target A1C of less than 7.0% (93% to 97% tirzepatide participants versus 34% placebo), an A1C of less than 6.5% (80% to 95% tirzepatide participants versus 17% placebo) or an A1C of less than 5.7% (26% to 62% tirzepatide participants versus 3% placebo).

Forty-one serious adverse events were identified throughout the study; 9 (8%) in participants that received 5 mg tirzepatide, 13 (11%) in participants that received 10 mg tirzepatide, 9

(8%) in participants that received 15 mg tirzepatide, versus 10 (8%) in insulin glargine. No deaths occurred in trial participants. The most common adverse events were gastrointestinal, including diarrhea (12% to 21% tirzepatide versus 10% placebo), nausea (13% to 18% tirzepatide versus 3% placebo), and vomiting (7% to 13% tirzepatide versus 3% placebo). Hypoglycemia (< 3 mmol/L) was reported in 18 (15.5%) participants that received 5 mg tirzepatide, in 23 (19.3%) in participants that received 10 mg of tirzepatide. and in 17 (14.2%) in participants that received 15 mg of tirzepatide, compared to 15 (12.5%) who received placebo.

Concurrent Developments

Phase III clinical trials without data available or currently in progress are summarized in Table 2. SURPASS J-mono[22] is a trial determining the glycemic efficacy and safety of tirzepatide compared to dulaglutide, a GLP-1 analogue, in participants with T2D from Japan. SURPASS J-combo[23] is a trial investigating the long-term safety of tirzepatide in combination with oral antihyperglycemic medications in patients with diabetes in Japan. SURPASS-AP-combo[24] is a trial comparing the glycemic efficacy of tirzepatide to insulin glargine in participants with T2D on metformin with or without sulfonylurea. The ongoing SURPASS-6[25] study is comparing the glycemic efficacy of tirzepatide once weekly versus insulin lispo (U100) 3 times daily in participants with T2D inadequately controlled on insulin glargine (U100) with or without metformin. To assess MACE, the SURPASS-CVOT[26] study is assessing the efficacy and safety of tirzepatide to dulaglutide in participants with T2D and increased cardiovascular risk.

Concurrent with assessing the efficacy of tirzepatide at reducing A1C in T2D, tirzepatide is also being investigated for treating obesity in those with/without T2D (SURMOUNT[33-37] studies) and heart failure (SUMMIT[38] study).

Considerations for Future Uptake

Cardiovascular Benefit

T2D enhances the progression of cardiovascular diseases, leaving patients with T2D at a heightened risk for major adverse cardiovascular events (MACE).[4,39] SURPASS-4[18] evaluated the glycemic efficacy and cardiovascular safety of tirzepatide for 52 weeks compared to insulin glargine in participants with T2D at heightened risk of cardiovascular diseases. A meta-analysis of the SURPASS studies suggests that tirzepatide does not increase the risk of MACE in participants with T2D.[40] However, trials assessing longer-term major averse cardiovascular events are still ongoing (SURPASS-CVOT[26]). Based on available evidence,[41] Diabetes Canada's clinical practice guidelines for the prevention and management of diabetes already recommends some GLP-1 receptor agonists alone or SGLT2 inhibitors for longer-term cardio- and renal benefits.[6] Pending the availability of longer-term data on cardiovascular outcomes and the completion of the SURPASS-CVOT study in 2024,[26] uptake of tirzepatide for cardiovascular benefits may likely be limited.

Table 2: Characteristics of Ongoing Phase III Randomized Clinical Trials

Name of study, NCT number, study completion date	Study design Study duration Sample size	Population	Intervention(s) Comparator(s)	Primary outcome(s)
Completed trials without data available				
SUPRASS J-mono (NCT03861052) **Completion date: March 2021**	Double blind 52 weeks N = 636	T2D If OAM naive, OAM A1C 7.0% to 10.0% If currently on OAM, A1C 6.5% to 9% BMI ≥ 23 kg/m^2 ≥ 3 months stable body weight, no exercise/ intensive diet for body weight reduction	Interventions: 5 mg tirzepatide weekly SC 10 mg tirzepatide weekly SC 15 mg tirzepatide weekly SC Comparator: Dulaglutide 0.75 mg	Mean change in A1C from baseline
SURPASS J-combo (NCT03861039) **Completion date: February 2021**	Open label 52 weeks N = 442	T2D A1C 7.0% to 11.0% ≥ 3 months sulfonylureas, metformin, thiazolidinedione, Alpha-glucosidase inhibitor, glinides, or SGLT2 inhibitor monotherapy BMI ≥ 23 kg/m^2 ≥ 3 months stable body weight, no exercise/ intensive diet for body weight reduction	Interventions: 5 mg tirzepatide weekly SC 10 mg tirzepatide weekly SC 15 mg tirzepatide weekly SC	Number of patients with ≥ 1 SAE
SURPASS-AP combo (NCT04093752) **Completion date: November 2021**	Open label 40 weeks N = 917	T2D ≥ 2 months treatment with metformin with/without sulfonylurea Insulin naive A1C 7.5% to 11.0% BMI ≥ 23 kg/m^2 ≥ 3 months stable body weight, no exercise/ intensive diet for body weight reduction	Interventions: 5 mg tirzepatide weekly SC 10 mg tirzepatide weekly SC 15 mg tirzepatide weekly SC Comparator: Insulin glargine	Mean change in A1C from baseline

Name of study, NCT number, study completion date	Study design Study duration Sample size	Population	Intervention(s) Comparator(s)	Primary outcome(s)
Ongoing trials				
SURPASS-6 (NCT04537923) **Estimated completion date: October 2022**	Open label 52 weeks N = 1,182	T2D A1C 7.5% to 11.0% ≥ 90 days treated with basal insulin with/without metformin, sulfonylureas, or DPP4 inhibitors ≥ 3 months stable body weight BMI ≥ 23 kg/m^2	Interventions: 5 mg tirzepatide weekly SC 10 mg tirzepatide weekly SC 15 mg tirzepatide weekly SC Comparator: Insulin lispo	Mean change in A1C from baseline
SURPASS-CVOT (NCT04255433) **Estimated completion date: October 2024**	Double blind Event driven N = 12,500	T2D Atherosclerotic cardiovascular disease A1C 7.0% to 10.5% BMI ≥ 25 kg/m^2	Interventions: tirzepatide weekly SC Comparator: Dulaglutide	Time to first occurrence of a component of event of MACE-3 (cardiovascular death, myocardial infarction, or stroke)

A1C = glycated hemoglobin; BMI = body mass index, DPP4 = Dipeptidyl peptidase-4; MACE = major adverse cardiovascular event; OAM = oral antihyperglycemic medication; RCT = randomized controlled trials; SAE = severe adverse event; SGLT-2 = sodium glucose cotransporter; T2D = Type 2 diabetes.

Target Population

Ethnicity is a significant risk factor for T2D.[2,42,43] Most SURPASS participants were white, with limited representation of minority populations. Indigenous peoples and communities of colour represent more than 20% of the Canadian population and have an increased prevalence of T2D.[2,42,43] Although race may influence the cardiovascular efficacy of other drugs, such as SGLT-2 inhibitors and GLP-1 agonists,[44,45] it is too early in clinical development to understand how the efficacy of tirzepatide might differ in different subpopulations.

SURPASS participants were on average 55 years of age and older. Although there is an increased frequency of T2D diagnosis occurring in children and adolescence,[46] no data are available at this time for this age demographic.

Cost

The prevalence of T2D is increasing in Canada[1] and newer drug classes to treat T2D contribute significantly to growth in public drug program spending in Canada.[47] Although the price of tirzepatide is currently not available, future cost-effectiveness studies will be necessary to determine if tirzepatide adds value to the existing drug classes already available in Canada.

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