TECHBRIEF

HORIZON SCANNING REPORT

TIRZEPATIDE FOR THE TREATMENT OF TYPE 2 DIABETES MELLITUS

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TechBrief

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SUMMARY

Tirzepatide is a once-weekly injectable medication for the treatment of type 2 diabetes mellitus (T2DM). This new glucose-lowering therapy is called a dual agonist or a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist. The glucose-dependent insulinotropic polypeptide is a hormone that may complement the effects of GLP-1 receptor agonists and it will potentially impose greater effects on glucose and body weight.[1] Tirzepatide was developed by Eli Lilly (United States). It is administered subcutaneously.[2]

The clinical efficacy, safety and tolerability of tirzepatide have been reported in phase 1 and phase 2 clinical trials.[2] It has been tested in more than 13,000 patients across 10 clinical trials and five of those trials were large global studies designed to support registration of the drug. Eli Lilly plans to submit a full registration package to regulators by the end of 2021.[3] Tirzepatide showed significantly better efficacy concerning glucose control and weight loss with mild to moderate gastrointestinal (GI) adverse events. However, the official results of the phase 3 trials need to be reviewed.

Keywords: Tirzepatide, Glucose-dependent insulinotropic polypeptide, Glucagon-like peptide-1, Diabetes mellitus, Type 2 diabetes

INTRODUCTION

Diabetes mellitus is a chronic disease that occurs when the pancreas does not produce enough insulin or when the body ineffectively uses the insulin it produces. Type 1 diabetes mellitus (T1DM) is characterised by a lack of insulin production and T2DM results from the body's ineffective use of insulin. About 90% of people with diabetes around the world have T2DM. It is largely the result of excess body weight and physical inactivity.

The prevalence of diabetes mellitus has been rising more rapidly in low- and middle-income countries than in high-income countries. Diabetes is a major cause of blindness, kidney failure, heart attacks, stroke and lower limb amputation. Between 2000 and 2016, there was a 5% increase in premature mortality from diabetes. In 2019, an estimated 1.5 million deaths were directly caused by diabetes.[4]

Overall diabetes prevalence in Malaysian adults ≥18 years as reported in NHMS 2015 and 2019 were 13.4% and 18.3% respectively. Prevalence in overall diabetes for adults age 30 years and above was 24.1% in NHMS 2019. Prevalence of overall diabetes among the major ethnic groups in the NHMS 2019 showed a similar trend as previous data which was 31.4%, 22.6% and 15.1% among the Indians, Malays and Chinese, respectively.[5]

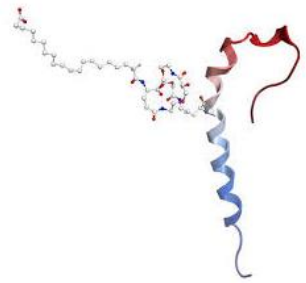
Prevalence of a known or established diagnosis of diabetes during the 2019 NHMS was 9.4%, whilst in 2015 it was 8.3%. Hence in 2019, there were almost 2 million (1,999,450) adult individuals with known diabetes in Malaysia.[5]

The National Health and Morbidity Survey (NHMS) 2019 reported at the time of the survey, the prevalence of abnormal fasting plasma glucose (FPG) in the non-diabetic range (FPG 5.6 - 6.9 mmol/L) was 23.6%. These estimates affected approximately 5 million (5,019,359) adult individuals in Malaysia with probable pre-diabetes in 2019 and future risk of diabetes. Prevalence of unknown/undiagnosed diabetes (elevated FPG of ≥7.0 mmol/L during the survey) for adults aged ≥18 years were 5.1% in 2015 and 8.9% in 2019. In 2019, there was an estimated 1,892,515 adult individuals with unknown/undiagnosed diabetes in Malaysia.[5]

Type 2 diabetes mellitus may be managed with oral and injectable medications, insulin, weight reduction, or dietary changes. The choice of medications for T2DM is individualised, taking into account the effectiveness and safety profile of each medication, the patient's underlying health status, any medication compliance issues, and cost to the patient or healthcare system. Medications for T2DM can work in different ways to reduce blood glucose levels. They may increase insulin sensitivity and glucose excretion. They may also decrease absorption of carbohydrates from the digestive tract, or work through other mechanisms. Medications for T2DM are often used in combination. Different methods of delivering insulin include syringes, pre-filled pens, and insulin pumps.

THE TECHNOLOGY

Tirzepatide is a novel investigational once-weekly dual GIP and GLP-1 receptor agonist that integrates the actions of both incretins into a single molecule, representing a new class of medicines for the treatment of T2DM. The glucose-dependent insulinotropic polypeptide is a hormone that may complement the effects of GLP-1 receptor agonists. In preclinical models, GIP is being developed as weight reduction therapy as it has been shown to decrease food intake and increase energy expenditure. Furthermore, when it is combined with a GLP-1 receptor agonist, it will potentially impose greater effects on glucose and body weight.[1]



The tirzepatide molecule is a 39 amino acid linear peptide conjugated to a C20 fatty acid moiety. Tirzepatide image from Lilly.

Tirzepatide was developed by Eli Lilly (United States), formulated as a synthetic linear peptide containing 39 amino acids, based on the native GIP sequence. It is attached to a 20-carbon fatty diacid moiety, which binds to albumin, prolonging its half-life to five days and thus enabling once-weekly dosing. Tirzepatide has a comparable GIP receptor binding affinity to native GIP and five times lower GLP-1 receptor affinity than that of native GLP-1. Tirzepatide is administered subcutaneously.[2]

The clinical efficacy, safety and tolerability of tirzepatide has been reported in phase 1 and phase 2 clinical trials.[2] The latest study was the largest clinical trial for tirzepatide, as it has been tested in more than 13,000 patients across 10 clinical trials. Five of those trials were large global studies designed to support the registration of the drug. Eli Lilly plans to submit a full registration package to regulators by the end of 2021.[3]

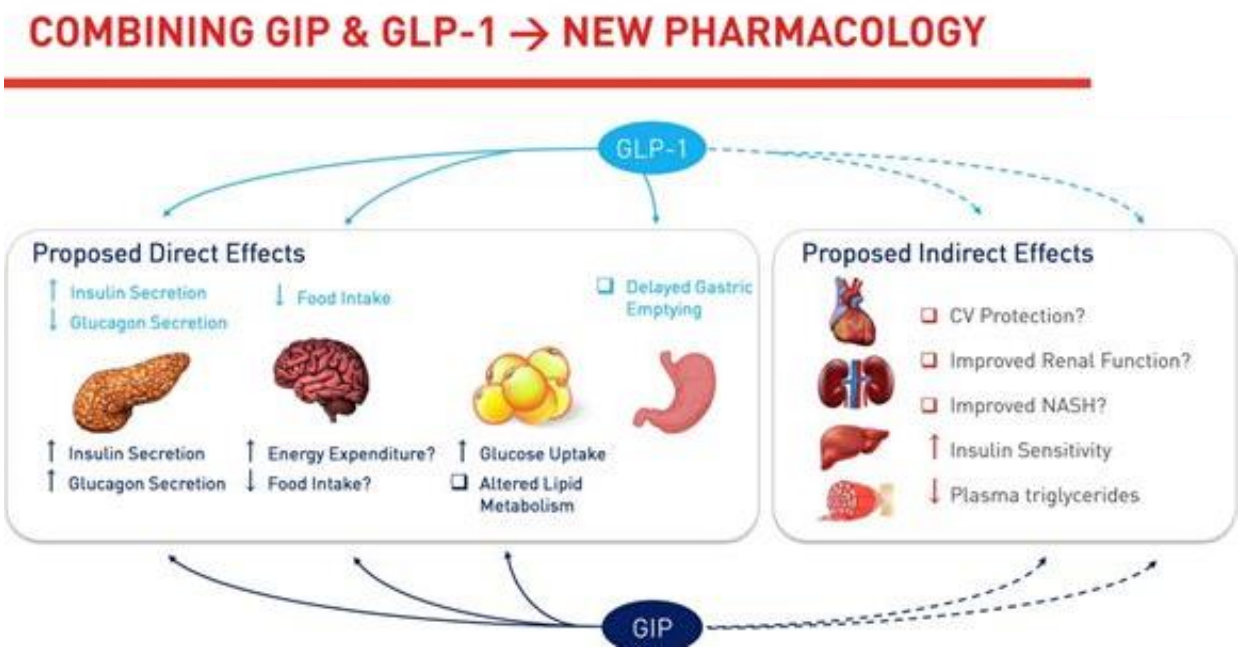


Figure 1. Tirzepatide's Potential Mechanism of Action

PATIENT GROUP AND INDICATION

Tirzepatide is indicated for patients with T2DM and obesity.

CURRENT PRACTICE

In Malaysia, treatment options in treating T2DM is as below:[5]

Medications	Mechanism of Action
Biguanides ○ Metformin	• Metformin lowers blood glucose especially FPG by decreasing hepatic glucose production. • Metformin reduces glycated haemoglobin (HbA1c) by up to 1.5% • Metformin is weight neutral or may result in mild weight loss of up to 1.1 kg

Sulphonylureas (SU) ○ Glibenclamide ○ Gliclazide ○ Glipizide (not in MoH formulary) ○ Glimepiride (not in MoH formulary)	• SUs reduce plasma glucose by increasing insulin secretion with an average HbA1c reduction of 0.46% - 1.62%. • The major adverse effect is hypoglycaemia. The risk is higher in renal impairment, liver cirrhosis and the elderly. • Weight gain in the range of 1.31 - 3.32 kg is common.
Meglitinides ○ Repaglinide (not in MoH formulary)	• Meglitinides are short-acting insulin secretagogues that bind to different sites within the SU receptor. It has a shorter half-life than SUs. • It is primarily used to control postprandial glucose (PPG) and reduces HbA1c by 1.0% - 1.2%. • It is associated with less risk of weight gain compared to SUs and hypoglycaemia may be less frequent.
Alpha-glucosidase inhibitors (AGIs) ○ Acarbose	• AGIs reduces the rate of absorption of polysaccharides in the proximal small intestine by inhibiting α-glucosidase enzymes. They should be taken with the main meals. • It lowers PPG without causing hypoglycaemia and reduces HbA1c by 0.5% - 0.8%.
Thiazolidinediones (TZD) ○ Pioglitazone (not in MoH formulary)	• TZDs are peroxisome proliferator-activated receptor-gamma (PPAR-γ) agonists and act primarily by increasing insulin sensitivity in muscle, adipose tissue and liver. • TZDs reduce HbA1c by 0.5% - 1.4%. • Improvement in glycaemic control may only be seen after six weeks with maximum effect at six months. • Side effects include weight gain, fluid retention, heart failure, macular oedema and osteoporosis.

Incretins ○ Dipeptidyl peptidase 4 inhibitors (DPP4-i) ▪ Sitagliptin ▪ Vildagliptin ▪ Saxagliptin ▪ Linagliptin (not in MoH formulary) ○ Glucagon-like peptide-1 (GLP-1) analogue (not in MoH formulary) ▪ Exenatide ▪ Liraglutide ▪ Lixisenatide ▪ Dulaglutide ▪ Semaglutide	• After meals, incretins (GLP-1 and glucose-dependent insulinotropic polypeptide [GIP]) are released and these augments glucose-induced insulin secretion and suppress glucagon release. Thus, it will reduce hepatic glucose output and plasma glucose in a glucose-dependent manner. • Incretins, at pharmacological levels, reduce gastric motility (slowing glucose absorption) and increase satiety by acting on centres in the brain. • The incretin effect is markedly decreased in T2DM, resulting in delayed and reduced insulin release as well as lack of suppression of glucagon release after a meal. • DPP4-i lower HbA1c by 0.5% - 0.8%. They are weight neutral and have a minimal risk of hypoglycaemia. • Currently, all available GLP1-RAs are in the form of injectables. GLP-1 RAs include exenatide IR and ER (once weekly), liraglutide (daily) and lixisenatide (daily) and, the once-weekly agents' dulaglutide and semaglutide. • GLP-1RAs have been shown to reduce HbA1C (~0.8% - 1.6%) and body weight (~1.0 - 4.1 kg). Their effects are dose-dependent. The weight reduction is due to the effect on satiety and delay in gastric emptying. • Common side effects of all GLP1-RAs are mainly gastro-intestinal i.e. nausea, vomiting and diarrhoea.

Sodium-glucose Cotransporter 2 inhibitors (SGLT2-i) (not in MoH formulary) ○ Dapagliflozin ○ Canagliflozin ○ Empagliflozin ○ Luseogliflozin ○ Ertugliflozin	• This class of drugs selectively inhibits SGLT2, a transporter in the proximal tubule, thus reducing glucose reabsorption leading to an increase in urinary glucose excretion. • It reduces HbA1c by 0.5% - 1.0%. • Additional effects of treatment include weight loss (1.8 - 2.7 kg) and reduction of systolic blood pressure (SBP) (2.7 - 4.8 mmHg) and diastolic blood pressure (DBP) (1.8 - 2.0 mmHg).

SAFETY & EFFICACY

Electronic searches were performed in Medline, EBM Reviews, EMBASE via OVID and PubMed, by using various combinations of the keywords tirzepatide, glucose-dependent insulinotropic polypeptide, glucagon-like peptide-1, diabetes mellitus, type 2 diabetes. In addition, Google was used to search for additional web-based materials and information. The last search was conducted on 9 July 2021. There were five randomised controlled trials included in this review.

A) Efficacy

The phase 3 trials test tirzepatide as monotherapy, or as an add-on to other treatments, and against established glucose-lowering drugs in people with type 2 diabetes, as well as a weight-loss agent in people with diabetes and obesity.

To date, there are more than five trials conducted which include different types of population and comparator treatment. However, only five trials were completed and the details are as below:

SURPASS-1[6]	
Population	Adult participants (≥18 years) with type 2 diabetes inadequately controlled by diet and exercise alone and also naive to injectable diabetes therapy
Comparator Treatment	Placebo
Status	Completed, published
Methods	Participants were randomly assigned (1:1:1:1) via computer-generated random sequence to once a week tirzepatide (5, 10, or 15 mg), or placebo. All participants, investigators, and the sponsor were masked to treatment assignment.
Results	At 40 weeks, all tirzepatide doses were superior to placebo: • Mean HbA1C reduction: 1.87% (5 mg), 1.89% (10 mg), 2.07% (15 mg), +0.04% (placebo) - estimated treatment differences versus placebo: -1·91% (5 mg), -1·93% (10 mg), and -2·11% (15 mg) (all p<0·0001)

	• Percentage of participants achieving HbA1C less than 7%: 87 - 92% (all tirzepatide doses), 20% (placebo) • Percentage of participants achieving HbA1C less than 6.5%: 81 - 86% (all tirzepatide doses), 10% (placebo) • Percentage of participants achieving HbA1C less than 5.7%: 31 - 52% (all tirzepatide doses), 1% (placebo) • Weight reduction: 7 - 9.5 kg (all tirzepatide doses)

SURPASS-2[7]	
Population	Participants with type 2 diabetes and taking metformin monotherapy
Comparator Treatment	Semaglutide
Status	Completed, published
Methods	In SURPASS-2, tirzepatide at the same three weekly doses (5, 10, and 15 mg) was tested against weekly injections of the GLP-1 receptor agonist semaglutide 1.0 mg.
Results	All three doses of tirzepatide delivered superior HbA1C and body weight reductions compared to semaglutide as showed: • HbA1C reduction: 2.01% (5 mg), 2.24% (10 mg), 2.30% (15 mg), 1.86% (semaglutide) - the treatment differences versus placebo: -0.15%, p=0.02 (5mg), -0.39%, p<0.001 (10mg), -0.45%, p<0.001 (15mg) • Percent of participants achieving HbA1C less than 7%: 82.0% (5 mg), 85.6% (10 mg), 86.2% (15 mg), 79.0% (semaglutide) • Percent of participants achieving HbA1C less than 6.5%: 69 - 80% (all tirzepatide doses), 64% (semaglutide) • Percent of participants achieving HbA1C less than 5.7%: 27.1% (5 mg), 39.8% (10 mg), 45.7% (15 mg), 18.9% (semaglutide) • Weight reduction: 7.6 kg (5 mg), 9.3 kg (10 mg), 11.2 kg (15 mg), 5.7 kg (semaglutide) (p<0.001) At the highest dose, it achieved an average 2.46% HbA1c reduction and a 12.4 kg (13.1%) weight reduction, compared with 1.86% and 6.2 kg (6.7%), respectively, with semaglutide.

SURPASS-3[8, 9]	
Population	People taking metformin with/without an SGLT2-i
Comparator Treatment	Insulin degludec
Status	Completed, not yet published
Methods	In this trial, the investigators compared the efficacy of weekly tirzepatide (5, 10, and 15 mg) with daily insulin degludec in people with poorly controlled blood glucose despite stable treatment with metformin with or without an SGLT2-i.
Results	Each of the tirzepatide doses led to HbA1C and body weight reductions versus titrated insulin degludec:

	• HbA1C reduction: 1.85% (5 mg), 2.01% (10 mg), 2.14% (15 mg), 1.25% (insulin degludec) • Weight change: -7.0 kg (5 mg), -9.6 kg (10 mg), -11.3 kg (15 mg), +1.9 kg (insulin degludec) • Percent of participants achieving HbA1C <7%: 79.2% (5 mg), 81.5% (10 mg), 83.5% (15 mg), 58.0% (insulin degludec) Participants on the highest tirzepatide dose achieved an average 2.37% reduction in HbA1c after 52 weeks of treatment, which was significantly more than the 1.34% reduction for those taking degludec. Participants in the tirzepatide group lost an average of 12.9 kg, whereas the degludec group gained 2.3 kg, on average.

SURPASS-4[10]	
Population	People at increased cardiovascular risk, taking metformin with/without an SGLT2-i
Comparator Treatment	Insulin glargine
Status	Completed, published
Methods	The trial enrolled people with increased cardiovascular risk, with more than 85% of participants having previous events.
Results	At the highest dose tested (15 mg once a week) tirzepatide: • reduced HbA1c by 2.58%, compared to 1.44% for insulin glargine • reduced weight 11.7 kg averaged over a year, while the control group gained 1.9kg • 43% of patients achieved an HbA1C less than 5.7%

SURPASS-5[8, 9]	
Population	People taking insulin glargine
Comparator Treatment	Placebo
Status	Completed, not yet published
Methods	The SURPASS-5 trial-tested tirzepatide (5, 10, and 15 mg) in people with insulin-dependent type 2 diabetes with uncontrolled blood glucose despite treatment with insulin glargine, with or without metformin.
Results	Each of the tirzepatide doses led to HbA1C and body weight reductions compared to placebo: • HbA1C reduction: 2.11% (5 mg), 2.40% (10 mg), 2.34% (15 mg), 0.86% (placebo) • Weight reduction: 5.4 kg (5 mg), 7.5 kg (10 mg), 8.8 kg (15 mg), +1.6 kg (placebo) • Percent of participants achieving HbA1C <7%: 87.3% (5 mg), 89.6% (10 mg), 84.7% (15 mg), 34.5% (placebo) At the highest tirzepatide dose, there was a significant reduction in HbA1c (2.59% on average) compared to the placebo group

	(0.93%). Weight reduction in the tirzepatide group is 10.9 kg on average, whereas the placebo group gained 1.7 kg on average.

B) Safety

The most commonly reported adverse events were gastrointestinal (GI) - related with mild to moderate in severity, and usually occurring during the dose-escalation period and decreasing with continued dosing. The prevalence of adverse events ranged as below:[6, 7, 9, 10]

- nausea (12 - 23.7%) in all tirzepatide groups compared to placebo group (2.5 - 6.1%), semaglutide group (18%) and insulin degludec group (1.7%)
- diarrhoea (12 - 20.8%) in all tirzepatide groups compared to placebo group (8 - 10.0%), semaglutide group (12%) and insulin degludec group (3.9%)
- vomiting (2 - 12.5%) in all tirzepatide groups compared to placebo group (2 - 2.5%), semaglutide group (8.3%) and insulin degludec group (1.1%)
- constipation (5.8 - 6.7%) in all tirzepatide groups compared to placebo group (0.9 - 1.7%) and semaglutide group (0.9%)

Treatment discontinuation rates due to adverse events were 5.1 - 10.9% in all tirzepatide groups compared to 2.5% in the placebo group, 3.8% in the semaglutide group and 1.4% in the insulin degludec group.[7, 9]

COST

There was no retrievable data on the cost of tirzepatide. However, it was estimated to be the same as GLP-1 analogue which is around USD700 to USD850 (MYR2,897 to MYR3,518; conversion rate = 4.139) per pen or for 2.4 mL vial where it can last for a month's use depending on the dose given.[11, 12, 13]

ORGANISATIONAL ISSUES

There was no organisational issue identified.

SOCIETAL/ETHICAL ISSUES

There was no societal or ethical issue identified.

POTENTIAL IMPACT

In conclusion, tirzepatide showed significantly better efficacy concerning glucose control and weight loss in T2DM patients with mild to moderate GI adverse events. Nevertheless, the official results of the phase 3 trials need to be reviewed once it is fully published.

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