easternhealth

Participant Information Sheet/Consent Form

Box Hill Hospital

Title	The Effect of Tirzepatide versus Dulaglutide on Major Adverse Cardiovascular Events in Patients with Type 2 Diabetes
Short Title	SURPASS-CVOT
Protocol Number	I8F-MC-GPGN
Study Sponsor	Eli Lilly Australia Pty Ltd
Principal Investigator	A/Professor Richard Simpson
Location	Box Hill Hospital – Arnold Street, Box Hill VIC 3128, Australia

Part 1 What does my participation involve?

1 Introduction

You are invited to take part voluntarily in a research study of a study drug known as tirzepatide (also known as LY3298176). This is because you have type 2 diabetes with established cardiovascular disease. The research study is testing the potential new efficacy of tirzepatide in preventing cardiovascular events induced by type 2 diabetes.

This Participant Information Sheet and Consent Form tells you about the research study. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the study.

Please read this information carefully. Ask questions about anything that you do not understand or want to know more about. Before deciding whether to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this study is voluntary. If you do not wish to take part, you do not have to. You will receive the best possible care whether you take part.

If you decide you want to take part in the study, you will be asked to sign the consent section. By signing it you are telling us that you:

- Understand what you have read
- Consent to take part in the study
- Consent to have the tests and treatments that are described
- Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information Sheet and Consent Form to keep.

2 What is the purpose of this study?

The main reason for you to take part in this study is to help in answering the following research question:

- How tirzepatide compares to dulaglutide (Trulicity) in preventing cardiovascular events in participants with type 2 diabetes and a higher risk of cardiovascular events (you may benefit from medications that either do not increase this risk or prevent new serious cardiovascular complications).

Tirzepatide is an experimental treatment. This means that it is not an approved treatment for type 2 diabetes in Australia.

This research is being conducted and sponsored in Australia by Eli Lilly Australia Pty Ltd.

3 What does participation in this study involve?

Before any study assessments and procedures are performed, you will be asked to sign the consent form. The study staff will discuss with you what is required for you to be part of this study. You may need to have some tests or checks done to find out if you are suitable.

The duration of your participation depends on how long it takes for 1615 participants to experience a certain major cardiovascular event (including heart attack, stroke, or cardiovascular death), which may be up to 5 or 6 years. You will receive study drug until the end of the study, until you cannot tolerate the study drug, or if you and/or your doctor wish to stop the study drug. If you stop the study drug before the study ends, you will be asked to continue attending study visits to monitor your health and restart study drug later if possible.

You will be screened to see if you meet the requirements to be in the study.

You will be randomised to receive either an increasing dose of tirzepatide (up to 15 mg) or dulaglutide (Trulicity, 1.5 mg). You have an equal chance of receiving either medicine. Neither you nor the study doctor will know which medicine you are taking. You will inject the medicine subcutaneously once a week.

You will be trained on how to give yourself injections. If you are not able to give yourself injections, you may be allowed to have someone else trained to give you injections.

If you are in the tirzepatide group, you will receive the lowest possible dose of study drug at Visit 2. The dose will be raised every 4 weeks until you reach the maximum dose (15 mg) or until you experience intolerable stomach or intestinal problems, such as nausea, vomiting, or diarrhoea. If you have these side effects, you will remain on the highest dose you can tolerate until Visit 16. In order to maximize treatment effect, if this occurs, you will be asked if you want to try to raise your dose again at Visit 16. If so, you will need to come in for additional visits in between your scheduled visits to continue raising your dose. These visits will occur every 4 weeks until you reach the maximum dose (15 mg) or the highest dose you can tolerate. If you decline, you will continue on the same dose and your 3-month visit schedule.

If you are in the dulaglutide (Trulicity) group, you will remain on the same dose (1.5 mg) throughout the study, starting at Visit 2. However, an imitation dose escalation and de-escalation will be used to make sure you do not know which drug you are receiving. If you experience intolerable stomach or intestinal problems, imitation dose de-escalation will be performed. Even though you will remain on the same dulaglutide dose (1.5 mg/week) for the imitation dose de-escalation, stomach or intestinal problems on dulaglutide usually get better and disappear after a short period of time. If the imitation dose de-escalation occurs, you will be asked if you want to try to raise your dose again at Visit 16. If so, you will need to come in for additional visits in between your scheduled visits to continue imitation dose escalation. These visits will occur every 4 weeks until you reach the maximum imitation escalation or the highest imitation escalated dose you can tolerate. If you decline, you will continue on your 3-month visit schedule.

You will continue injecting the study drug until at least 1615 participants experience a certain major cardiovascular event (including heart attack, stroke, or a cardiovascular event).

Even if you stop the study drug before the study ends, you will be asked to continue attending study visits to monitor your health and restart study drug later if possible. At a minimum, the study doctor or staff will stay in contact with you by phone until the end of the study.

This study has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids study doctors or participants jumping to conclusions.

There are no additional costs associated with participating in this study, nor will you be paid. All medication, tests and medical care required as part of the study will be provided to you free of charge.

You may have to pay for some medicines according to hospital policy. You will be reimbursed for any reasonable travel and parking expenses associated with study visits. If you withdraw from the study early, you will be paid for these expenses for the portion of the study that you did complete. If you would like more details, please ask the study team.

If you decide to participate in this study, the study doctor will inform your local doctor.

Please read study procedures that are described in I8F-MC-GPGN Study Procedures, which you can find at the end of the document. This will give you information about what taking part in the study will mean to you, for example, how often you are required to come to see the doctor/nurse, how long each visit may take, how much blood will be taken and when tests and procedures will be performed.

If you are not able to attend a planned study visit or maintain telephone contact, the study doctor or staff may try to contact you to check on your health status and to see if you have experienced a serious health event. The study doctor or staff may try to locate you and search for your information by making contact with a family member, your family doctor, and hospitals or clinics that treat you. The study doctor or staff will try to contact you unless you withdraw consent of getting contacted further. Attempts to determine your health status may also be done by searching public records such as national registries or databases and voter records, if not prohibited by your local laws and regulations.

If you move or lose contact with the study doctor and staff, they may give your name and last known contact information to a patient locator service to try to find your current information, if not prohibited by your local laws and regulations. The patient locator service will not contact you directly and any new information they find will be shared with the study doctor and staff.

Following the study, the study doctor or one of the staff members may contact you to obtain information regarding the status of your health and quality of life.

4 What do I have to do?

The study doctor or a member of the study staff has discussed with you the requirements for participation in this study. It is important that you are open and honest with the doctor and staff about your health history. You cannot take part in this study if you do not meet all qualifications.

You can take part in this study if:

- You are at least 40 years old.
- You have been diagnosed with type 2 diabetes.
- You have certain types of cardiovascular disease, which your study doctor will discuss with you.
- You are willing to give yourself injections or have someone who would be willing to give you injections.

You cannot take part in this study if:

- You have certain other diseases, which your study doctor will discuss with you.

- You have had at least 1 event of severe low blood sugar within 6 months before screening.
- You have severe heart failure or have been hospitalised due to heart failure within 2 months prior to screening.
- You have had a certain type of stroke within 60 days before screening. Your study doctor will discuss this with you.
- You have had a certain blood vessel surgery within 60 days before screening, or you are planning to have one. Your study doctor will discuss this with you.
- You have had a certain kind of amputation within 60 days before screening, which your study doctor will discuss with you.
- You have a history of pancreatitis.
- You have type 1 diabetes.
- You have a history of advanced retinopathy (damage to blood vessels of your eyes).
- You have had gastric bypass surgery.
- You have hepatitis.
- You have a transplanted organ other than a certain type of eye transplant, which your study doctor will discuss with you.
- You have or have had evidence of cancer. Exceptions to this could be cancers in remission longer than 5 years, certain types of skin cancers, or a certain stage of cervical cancer or prostate cancer. Your study doctor will discuss this with you.
- You have a family or personal history of a certain type of thyroid cancer. Your study doctor will discuss this with you.
- You are pregnant or breastfeeding.

You must not participate in the study if you are pregnant or trying to become pregnant, or breast-feeding. If you are female and child-bearing is a possibility, you will be required to undergo a pregnancy test prior to commencing the study.

You agree to use the study drug only as instructed by your study doctor and staff, and to return any unused study drug (and empty containers) at each visit and at the end of your participation in the study or as instructed by the study doctor.

There may be unknown risks of possible harmful interaction with other medication you may be taking. You should follow the doctor's directions for taking this study drug carefully and you should not give the study drug to other people and should keep it out of the reach of small children.

You will be given supplies to monitor your blood glucose yourself.

You should continue your usual exercise habits and generally follow a healthy diet throughout the course of the study.

You should not donate blood or blood products during the study and for 8 weeks after the study ends.

You should return unused study drug at each visit.

Confidentiality of Trial Information

The information in this informed consent document is intended to help you determine whether participating in this study is right for you. You may wish to discuss this information with others for the purposes of helping you decide whether to participate in the study or as needed for medical treatment. You are asked to treat this information as confidential and to inform any others with whom you share this information that it is confidential. During the course of this study, you and/or a family member or caregiver of yours may learn, or have access to, proprietary information of the Sponsor, including drug product information. Proprietary information should be maintained as confidential. Please ask your study doctor for more specifics if you have a question about the

nature of any particular information.

5 Other relevant information about the study

Up to 12,500 participants will be taking part in this study worldwide. Up to 400 participants will be taking part in this study in Australia.

6 Do I have to take part in this study?

Your taking part in this study is entirely voluntary. You may refuse to take part in the study, or you may stop taking part in the study at any time without giving reasons, and without a penalty or loss of benefits to which you are otherwise entitled.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with Eastern Health.

7 What are the alternatives to participation?

You do not have to take part in this study to be treated for your condition. Other treatments for your condition are available. The current standard of care for type 2 diabetes is diet and exercise with 1 or more medications.

Your other choices may include:

- Medications such as sodium-glucose co-transporter 2 (SGLT-2) inhibitors and/or glucagon-like peptide-1 (GLP-1) receptor agonist depending on your health.
- Insulin or other glucose lowering drugs.
- Special diet or other lifestyle changes.
- Getting treatment or care for your type 2 diabetes without being in a study.
- Getting no treatment.

8 What are the possible benefits of taking part?

Although tirzepatide is being tested as a possible treatment for a condition that you have, you may not receive any medical benefit.

You may receive information about your health from any physical examinations and laboratory tests to be done in this study. People with type 2 diabetes and other people in the future may benefit through information gained from this study.

Study drug and study procedures will be provided at no cost to you.

9 What are the possible risks and disadvantages of taking part?

Medical treatments often cause side effects. You may have none, some or all the effects listed below, and they may be mild, moderate or severe. If you have any of these side effects or are worried about them, talk with your study doctor. Your study doctor will also be looking out for side effects.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell your study doctor immediately about any new or unusual symptoms that you get.

Many side effects go away shortly after treatment ends. However, sometimes side effects can be

serious, long lasting or permanent. If a severe side effect or reaction occurs, your study doctor may need to stop your treatment. Your study doctor will discuss the best way of managing any side effects with you.

Risks and discomforts associated with tirzepatide

As of 15 June 2018, 338 adults with type 2 diabetes (T2DM) and 67 healthy adults have taken tirzepatide in completed studies. Many of these patients were considered overweight or obese. Lilly has reviewed safety information from these studies.

The following table lists the risks and discomforts associated with tirzepatide for patients with T2DM.

Very Common (10 or more out of 100 people)	Feeling sick to the stomach (nausea) Loose or frequent stools (diarrhoea) Throwing up (vomiting) Loss of appetite	
Common (1 or more out of 100 people)	Headache Dizziness Indigestion Heartburn Feeling tired, fatigue Hard or infrequent stools	Passing gas Bloating Belching Stomach pain or discomfort Weight loss Low blood sugar
Uncommon (1 or more out of 1000 people)	Feeling full quickly when eating	

Cases of pancreatitis have been reported in patients with T2DM who have taken tirzepatide and other glucagon-like peptide-1 receptor (GLP-1) medicines. Pancreatitis is an inflammation of the pancreas, a gland in your abdomen that helps with digestion. Pancreatitis is usually associated with stomach pain, which may be severe. Although pancreatitis usually improves without long-term effects, it may be severe and could lead to hospitalisation or even death.

If you develop abdominal pain that is not normal for you, or if you develop severe nausea with or without vomiting, you should call your study doctor immediately for evaluation and proper care. If you have pancreatitis symptoms or if routine laboratory tests suggest a need for evaluation, you may be asked to return to the study site for further evaluations, which may include additional blood tests, X-rays, or other abdominal pictures.

Symptoms of nausea, vomiting, and diarrhoea may lead to loss of fluids (dehydration). The loss of fluids could worsen kidney function, which includes kidney failure, and requires immediate evaluation by the study doctor for appropriate care.

Tirzepatide is not recommended for patients with severe stomach problems, such as slowed emptying of the stomach (gastroparesis) or problems with digesting food.

Increases in resting heart rate (HR) above the normal range (more than 100 beats per minute) have been seen in both healthy participants and patients with T2DM taking tirzepatide. Increased HR can have no symptoms or symptoms such as pounding heart, irregular or "skipped" heartbeat that you can feel, chest pain, or other more severe symptoms. Your heart rate and blood pressure will be checked throughout the study.

If you take tirzepatide with or without other medicines used to treat T2DM, your blood sugar could become too low (hypoglycaemia). While taking tirzepatide, you may be more likely to have low blood sugar if you are also taking insulin or an insulin secretagogue (sulphonylurea). It is important to follow the study doctor's recommendations for monitoring your blood sugar level during your participation in this study. You should tell the study doctor if you experience any symptoms of low blood sugar, such as sweating, hunger, shakiness, or confusion.

Cases of severe and potentially life-threatening allergic reactions have occurred rarely in patients taking other GLP-1 medicines and may be a potential side effect with tirzepatide. Tirzepatide should not be given to patients who have had a serious allergic reaction to tirzepatide or any of its ingredients.

Your body's disease protection system (immune system) may react to tirzepatide by making antibodies. Your study doctor may take blood samples during the study to check for antibodies to tirzepatide.

Very rarely, cases of medullary thyroid cancer were reported with other GLP-1 medicines. If you or anybody from your family (genetic relatives only) have had this type of cancer or another disease called multiple endocrine neoplasia syndrome type 2, please tell your doctor because you should not receive tirzepatide. Since you are participating in a long-term study with tirzepatide, your calcitonin levels will be measured to detect any potential medullary thyroid disease.

Additionally, it is possible that you could have other unknown side effects while taking tirzepatide.

You should not take tirzepatide if you are pregnant or may become pregnant. Female rats that were given tirzepatide had irregular menstrual cycles and body weight loss or decreased body weight gain or both. Pregnant rats and rabbits that were given tirzepatide and lost too much body weight had offspring that were smaller than normal. Some of these offspring had malformations (organ development abnormalities). Because tirzepatide has only been tested in pregnant animals, humans who take tirzepatide while pregnant may experience other unknown side effects.

Risks and discomforts associated with dulaglutide (Trulicity)

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Severe side effects

Rare	• Severe allergic reactions (such as, anaphylactic reactions [which are potentially life threatening, severe allergic reactions should

(may affect up to 1 in 1000 people)	always be treated as a medical emergency], angioedema [which is an area of swelling of the lower layer of skin and tissue just under the skin or mucous membranes]). You should see a doctor immediately if you experience symptoms such as rashes, itching, and rapid swelling of the tissues of the neck, face, mouth or throat, hives, and difficulties breathing. • Inflamed pancreas (acute pancreatitis) which could cause severe pain in the stomach and back which does not go away. You should see a doctor immediately if you experience such symptoms.
Not Known (the frequency cannot be estimated from available data)	• Bowel obstruction – a severe form of constipation with additional symptoms such as stomach ache, bloating, or vomiting. You should see a doctor immediately if you experience such symptoms.

Other side effects

Very Common (may affect more than 1 in 10 people)	• Feeling sick to the stomach (nausea) • Throwing up (vomiting) • Loose or frequent stools (diarrhoea) • Abdominal (stomach) pain These side effects are usually not severe. They are most common when first starting dulaglutide (Trulicity) but decrease over time in most patients. • Hypoglycaemia (low blood sugar) is very common when dulaglutide (Trulicity) is used with medicines that contain metformin, a sulphonylurea and/or insulin. If you are taking a sulphonylurea or insulin, the dose may need to be lowered while you use dulaglutide (Trulicity).
Common (may affect up to 1 in 10 people)	• Hypoglycaemia is common when dulaglutide (Trulicity) is used alone, or with both metformin and pioglitazone together, or with a sodium-glucose co-transporter 2 inhibitor (SGLT2i) with or without metformin. • Symptoms of low blood sugar may include headache, drowsiness, weakness, dizziness, feeling hungry, confusion, irritability, fast heartbeat, and sweating. Your doctor should tell you how to treat low blood sugar. • Feeling less hungry (decreased appetite) • Indigestion • Constipation • Gas (flatulence) • Bloating of the stomach • Gastroesophageal reflux disease - a disease caused by stomach acid coming up into the tube from your stomach to your mouth • Burping • Feeling tired • Increased heart rate • Slowing of the electrical currents in the heart
Uncommon	• Injection site reactions (e.g., rash or redness)

(may affect up to 1 in 100 people)	• Allergic reactions (hypersensitivity) (e.g., swelling, raised itchy skin rash [hives]) • Dehydration, often associated with nausea, vomiting, and/or diarrhoea • Gallstones • Inflamed gallbladder

Cases of severe and potentially life-threatening allergic reactions have been reported rarely in patients taking dulaglutide (Trulicity). Dulaglutide (Trulicity) should not be given to patients who have had a serious allergic reaction to dulaglutide (Trulicity) or to any of its ingredients.

Cases of pancreatitis have been reported in healthy participants and patients with type 2 diabetes who have received dulaglutide (Trulicity). Pancreatitis is an inflammation of the pancreas, a gland in your abdomen that helps with digestion. Pancreatitis is usually associated with persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting. If you develop abdominal pain that is not normal for you, or if you develop severe nausea with or without vomiting, you should call your study doctor immediately for evaluation and appropriate care. If you have pancreatitis symptoms or if routine laboratory tests suggest a need for further evaluation, you may be asked to return to the study site for further evaluations, which may include additional blood tests, x-rays, or other abdominal pictures.

Although pancreatitis usually improves without long-term effects, it may be severe and lead to hospitalisation and even death. Dulaglutide (Trulicity) has not been evaluated in patients with a prior history of pancreatitis. Cases of pancreatic cancer have been reported in patients with type 2 diabetes who have received dulaglutide (Trulicity). The effects of dulaglutide (Trulicity) on this cancer are not known.

Use of dulaglutide (Trulicity) may be associated with gastrointestinal adverse reactions, sometimes severe. Dulaglutide (Trulicity) is not recommended in patients with severe problems of the stomach, such as slowed emptying of stomach (gastroparesis) or problems with digesting food.

Symptoms of nausea, vomiting, and diarrhoea may lead to loss of fluids (dehydration), which could cause a worsening of kidney function including kidney failure requiring immediate evaluation by the study doctor and appropriate care.

In a cardiovascular outcomes trial of patients with type 2 diabetes with cardiovascular disease or multiple cardiovascular risk factors, diabetic retinopathy complications, which cause issues with the eyes, occurred in patients treated with dulaglutide 1.5 mg (1.9%) and placebo (1.5%). The proportion of patients with these complications was larger among patients with a history of diabetic retinopathy at baseline. In general, controlling glucose levels quicker has been associated with a temporary worsening of diabetic retinopathy. Your doctor should monitor you for diabetic retinopathy as part of your standard-of-care evaluations.

Increases in resting heart rate, sometimes above the normal range (that is, more than 100 beats per minute), have been observed in healthy participants and patients taking dulaglutide (Trulicity). Increases in your heart rate could lead to no symptoms or it could lead to symptoms such as pounding heart, irregular or “skipped” heartbeat that you can feel, chest pain, or other more severe symptoms. Your heart rate and blood pressure will be checked regularly.

If you take dulaglutide (Trulicity) with or without other anti-diabetic drugs, your blood sugar could be lowered too much (hypoglycaemia). The risk of hypoglycaemia is increased when dulaglutide (Trulicity) is used in combination with insulin secretagogues (e.g., sulphonylureas) or insulin. You may require a lower dose of sulphonylurea or insulin to reduce the risk of hypoglycaemia in this setting. It is important to follow the study doctor's recommendations for monitoring your blood sugar level during your participation in this study and to inform the study doctor if you experience symptoms of low blood sugar, such as sweating, hunger, shakiness, or confusion.

A case of medullary thyroid cancer was reported in a patient in a dulaglutide (Trulicity) study. This patient's calcitonin (a hormone in the blood that is high with this type of cancer) value was high prior to getting dulaglutide (Trulicity) study drug, suggesting the tumour was present before the study. The effects of dulaglutide (Trulicity) on this cancer are not known. Since you are participating in a long-term study with dulaglutide (Trulicity), your calcitonin levels will be measured to detect any potential medullary thyroid disease.

Cancerous and noncancerous tumours of the thyroid gland were observed in a 2-year study in rats treated with dulaglutide (Trulicity). Similar findings have been observed in rodent studies of other drugs that work like dulaglutide (Trulicity). The relevance of these rodent thyroid tumours to humans is not known. Studies of up to 12 months in monkeys treated with dulaglutide (Trulicity) did not show any increased numbers of thyroid tumours.

It is also possible that you could have side effects that we do not yet know about.

Dulaglutide (Trulicity) has not been tested in pregnant women. Studies in animals have shown problems with reproduction. You should not take dulaglutide (Trulicity) if you are pregnant or may become pregnant.

During the study, you will continue to take your current medication. Ask your study doctor about any risks that may be associated with your current medication(s). Your study doctor may suggest continuing the medication at the same dose or change the dose.

During the study, you may be advised to take medication to treat symptoms that may arise during the study. The study doctor will discuss any risks with you.

Blood Tests

For most people, needle punctures for blood draws do not cause any bad problems. However, sometimes they may cause bleeding, bruising, discomfort, infections and/or pain where you had the blood drawn. You may also feel dizzy.

Electrocardiograms (ECGs)

There is no pain or discomfort during an ECG; however, removing the pads may cause some irritation to your skin.

Subcutaneous Injection

For most people, needle punctures for subcutaneous shots do not cause any serious problems. Sometimes they may cause bleeding or bruising where the shot is given. Sometimes people complain of discomfort, infections and/or pain at the site of the shot. Infection may happen with

subcutaneous shots because the needle breaks the skin. Then germs can get into the skin underneath. Shots may cause abscesses or skin and soft tissue infections. Additionally, if a blood vessel is hit by the needle, the risk of infection will be even greater if germs are taken into the blood system.

Eye Exam

You may receive drops in your eyes during your eye exam that will dilate your pupils (small openings in the middle of your eyes). Dilated pupils may make it difficult for you to drive, work in bright light, or read for a while after your appointment.

In addition to the risks already described, tirzepatide, dulaglutide (Trulicity) and the study procedures may have other unknown risks. There may also be unknown risks to an embryo, foetus, or nursing child. The effects of tirzepatide and dulaglutide (Trulicity) on an unborn child or newborn baby are not known.

If you are female, you should not become pregnant or breastfeed a child while in this study. Naturally, the best way to not become pregnant is not to have vaginal sex (intercourse). You can practice total abstinence (if this is your preferred and usual lifestyle). You are not required to use contraception if you are a woman in exclusively same sex relationships (as your preferred and usual lifestyle). If you are sexually active, you must use 2 forms of effective birth control. You should talk with your doctor about the types of birth control that are best for you and your partner. Tell your doctor right away if you become pregnant or think you are pregnant.

If you are male, you should not father a baby while in this study. You should not have vaginal sex (intercourse) without using 2 forms of effective birth control. If you are a man in exclusively same sex relationships (as your preferred and usual lifestyle), you are not required to use contraception. Talk to your doctor about the types of birth control that might be best for you and your partner. Tell the doctor right away if your partner becomes pregnant or thinks she may be pregnant. Also, you should not donate semen/sperm.

Taking part in this study can result in risks to an unborn child or breastfeeding child. You must continue to use birth control for 30 days after the last dose of the study drug if you are a sexually active female or for 3 months after the last dose of the study drug if you are a sexually active male.

10 What will happen to my test samples?

Various blood and urine samples will be collected from you during this study. The specific procedures for collecting these samples and the risks associated with collection are explained in the procedure table and risks section in this document. Your samples will be identified by your study participant number, and not by your name.

The analysis of your samples may contribute to the creation of new laboratory tests, new medicines, or other items that may be commercially valuable to the sponsor. The sponsor has no plans to provide you, either now or in the future, any compensation, royalty, or any other financial benefit that might result from any product, procedure, or other item that may be developed from studying your sample(s) or any information or data that is derived from such research.

The samples obtained for the purpose of this study will be transferred to Covance Asia Pte Ltd. The samples may be moved for further analysis at the request or notification of the Sponsor, to another appropriate facility.

Samples for Study Qualification and Health Monitoring

Blood and urine samples will be collected to determine if you meet the requirements to participate in this study. Additional blood and urine samples will be collected throughout the study to monitor your health and your response to study drug.

Blood samples may be tested for hepatitis A, B, C, and/or E which are serious and contagious diseases. If your test results are positive, your study doctor or staff will contact you. The results of hepatitis A, B, C and/or E testing will be kept confidential and disclosed only as required by law.

All samples collected for Study Qualification and Health Monitoring **will be destroyed within 60 days of confirmation of the test results, unless laws, regulations,** or international **laboratory certification standards require a longer retention period.** This confirmation will either occur immediately after initial testing or may require that samples be held to be retested at a defined later point in time.

Samples for Measuring Study Drug Levels

If you experience an allergic reaction to the study drug, blood samples may be collected to measure the amount of study drug that is in your body and how your body breaks it down. The samples will be stored for a maximum of 1 year after this study is finished.

Samples for Genetic Research

Blood will be collected to study your DNA. DNA is genetic material that is found in all the cells of your body. DNA contains instructions that your body reads to understand how it should be built and work. Some of these instructions tell your body how to react to medicines. For this reason, looking at DNA can sometimes help explain why people with a disease respond differently to the same medicine. For example, some people taking this study medicine may respond well. Others may have little or no response or have side effects.

Researchers may study your DNA to learn how the study medicine works for you. Information about your DNA may be used to create or improve tests to measure these genetic factors. Researchers may also study your DNA to better understand the disease for which this study drug is developed.

The DNA sample may be stored for up to **15** years after this study is finished. The samples obtained for the purpose of this study will be transferred to Covance Asia Pte. Ltd, Singapore. The samples may be moved for further analysis at the request or notification of the Sponsor, to BioStorage Technologies Asia Pacific Pte. Ltd, Singapore.

Neither you nor the study doctor will obtain the results of these tests. This type of testing is done to further our knowledge about how the study drug works, and it will not produce the type of results that will have any useful meaning that would affect your health or treatment. Therefore, you will not be informed of the results of the tests.

The type of testing being done in this study is not testing that would result in information about a participant's future health or risk of having children with a genetic disorder, or information that may be relevant to the health of family members who are not part of the trial.

Samples for Antibody Research

If you experience an allergic reaction to the study drug, blood sample(s) may be collected to determine if your body produces antibodies against the study drug. Antibodies may affect how a

drug works in your body if you take it in the future. The sample(s) may be stored for up to **15** years after this study is finished.

Samples for Biomarker Research

Sometimes scientists measure substances in the body to diagnose, evaluate, or monitor a person's medical condition or disease. For example, cholesterol levels in the blood can be used to monitor a person's risk for heart disease. In this example, cholesterol is a biomarker.

Blood will be collected to identify or better understand biomarkers.

Researchers may use biomarkers to learn more about type 2 diabetes or how study participants respond to study drug or other medicines that you are taking during this study. Your sample(s) may also be used to create or improve tests to help identify study participants in the future who may respond to this study drug.

The sample(s) may be stored for up to **15** years after this study is finished.

11 What if new information arises during this study?

Sometimes during a research study, new information becomes available about the treatment that is being studied.

If any important new information is found during this study that may affect you wanting to continue to be part of this study, you will be told about it right away. If you decide to withdraw, your study doctor will make arrangements for your regular health care to continue. If you decide to continue in the study, you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research study. If this happens, your study doctor will explain the reasons and arrange for your regular health care to continue.

12 Can I have other treatments during this study?

Whilst you are participating in this study, you may not be able to take some or all the medications or treatments you have been taking for your condition or for other reasons. It is important to tell your study doctor and the study staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell your study doctor about any changes to these during your participation in the study. Your study doctor should also explain to you which treatments or medications need to be stopped for the time you are involved in the study.

It may also be necessary for you to take medication during or after the study to address side effects or symptoms that you may have. These medications will be provided to you at no cost.

13 What if I withdraw from this study?

If you decide to withdraw from the study, please notify a member of the study team before you withdraw. This notice will allow that person or the study supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the study, the study doctor and relevant study staff will not

collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the study can be measured properly and to comply with law. You should be aware that data collected by the sponsor up to the time you withdraw will form part of the study results. If you do not want them to do this, you must tell them before you join the study.

14 Could this study be stopped unexpectedly?

Your participation may be stopped by the study doctor or sponsor unexpectedly or without your consent for a variety of reasons. These may include reasons such as:

- Due to a bad reaction caused by tirzepatide or dulaglutide (Trulicity) you experience
- Due to new information about safety or effectiveness of either tirzepatide or dulaglutide (Trulicity)
- Tirzepatide being shown to work and not needing further testing
- Decisions made in the commercial interests of the sponsor or by local regulatory/health authorities.

If you stop being part of this study, the study doctor or one of the staff members will talk to you about any medical issues regarding the stopping of your participation.

15 What happens when the study ends?

Because this is a research study, the study drug will be given to you only during this study and not after the study is over. At the end of the study, your study doctor will discuss with you what treatment options are available.

A description of the study will be available at http://www.clinicaltrials.gov (NCT04255433). This website will not include any information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

At the end of the study you may receive the study results including any publication(s) (if applicable) on request from the study doctor.

Part 2 How is the study being conducted?

16 What will happen to information about me?

The study data sent by the study doctor to the sponsor does not include your name, address, or other information that directly identifies you. Instead, the study doctor assigns a participant number or code to the study data. Your personal information will be kept securely and will only be accessible by authorised personnel who have been trained in the handling of such confidential and sensitive information. Your study data will be retained for 15 year following the completion of the study.

The study doctor and staff will handle your personal health information in a confidential manner. Your personal health information will be stored in limited-access databases. Your health information will be used and disclosed in accordance with the Data Privacy Statement included with this document. Access to all information is limited and accessed only as indicated in this document. Steps are taken to reduce the risk of your personal health information being misused or accessed by unauthorised people. However, these risks cannot be eliminated.

Data Privacy Statement

As part of the conduct of this research study, it will be necessary to share medical information about you with persons other than the study doctor. This Data Privacy Statement explains how

your personal health information will be used and to whom it will be given ("disclosed") for this research study. It also describes your privacy rights, including your right to see your personal health information.

Your personal health information is information about you that could be used to identify you. For this research study, this includes information in your existing medical records needed for this study and new information created or collected during the study ("study data"). Information about your participation in this research project may be recorded in your health records.

The study doctor and staff will handle your personal health information in a confidential manner. All precautions will be taken to ensure that all information collected during this study will be handled in accordance with Australian privacy and other relevant laws.

By signing the consent form for this study, you will give permission ("authorisation") for the use and disclosure of your personal health information in the following ways:

- Your personal health information may be shared with or viewed by:
    - the study doctor and staff,
    - the sponsor and its representatives (referred to as the "sponsor"),
    - the regulatory authorities in this country and in other countries,
    - the human research ethics committee overseeing this study, and
    - doctors at other institutions participating in the study, whether in Australia or elsewhere.

- The sponsor may send your study data outside of this country and may also share your study data with their related companies and business partners.
- The sponsor will use the study data for research purposes:
    - to support the scientific objectives of the study described in the consent document,
    - to assess the safety or efficacy of any drug or treatment included in the study,
    - to better understand the disease(s) included in the study, or
    - to improve the design of future studies.
- Study data that does not identify you may be published.

You have the right to see and ask for a copy of your personal health information and ask for it to be corrected if you think it is wrong. If you would like to ask for a copy of your information, or to correct it or to make a complaint you can contact the study team member listed in Section 20 of this document. However, you may not be able to review some of the study data until after the study has been completed.

Your study data will be kept for as long as it is needed for legitimate business purposes according to the sponsor's records retention policies and applicable laws and regulations

You may cancel your authorisation for the use and disclosure of your personal health information at any time by providing written notice to the study doctor.

If you cancel your authorisation:

- The study doctor and staff will no longer use or disclose your personal health information in connection with this study.
    - However, the study doctor and staff may need to use or disclose some of your personal health information to confirm the accuracy of the study data.
- The sponsor will still use study data that was collected before you cancelled your authorisation.
- You will no longer be able to participate in the study.

17 Complaints and compensation

If you suffer any injuries or complications as a result of this research project, you should contact your study doctor as soon as possible for assistance with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

There are two avenues that may be available to you for seeking compensation if you suffer an injury as a result of your participation in this research project:

The pharmaceutical industry has set up a compensation process, which the Sponsor, Eli Lilly Australia Pty Ltd, of this research project has agreed to comply with. Details of the process and conditions are set out in the Medicines Australia Guidelines for Compensation for Injury Resulting from Participation in a Company-Sponsored Clinical Trial. In accordance with these Guidelines, the sponsor will determine whether to pay compensation to you, and, if so, how much. A copy of the Guidelines is available to you from the research staff on request. If you have any questions about the Guidelines, please contact the Manager of Eastern Health Office of Research & Ethics on (03) 9895 3398.

You may be able to seek compensation through the courts.

18 Who is organising and funding the study?

This study is being conducted, funded and sponsored in Australia by Eli Lilly Australia Pty Ltd.

The sponsor is paying Eastern Health for their work in this study.

19 Who has reviewed the study?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this study have been approved by Monash Health Human Research Ethics Committee.

This study will be carried out according to the *National Statement on Ethical Conduct in Human Research (2018* - incorporating all updates*)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

20 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this study or if you have any medical problems which may be related to your involvement in the study (for example, any injury, bad effect, or any other unusual health experience), you can contact the principal study doctor on (03) 9890 6472 or any of the following people:

Clinical contact person

Name	Gabrielle Garner
Position	Study Coordinator
Telephone	(03) 9094 9523
Email	Gabrielle.Garner@monash.edu

After-hours emergency:
For after-hours assistance (you can call at any time, day or night, to report emergency health experiences) please call the hospital switchboard on 1300 342 255 and ask for the Endocrinology registrar on call.

For matters relating to study at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person

Name	Eastern Health Office of Research & Ethics
Position	Manager
Telephone	(03) 9895 3398
Email	ethics@easternhealth.org.au

If you have any questions, concerns or complaints about your rights as a participant in a research study, please contact:

Reviewing HREC approving this study and HREC Executive Officer details

Reviewing HREC Name	Monash Health Human Research Ethics Committee
HREC Executive Officer	Ms Deborah Dell
Telephone	(03) 9594 4605
Email	research@monashhealth.org

Local HREC Office contact (Research Governance Officer)

Name	Eastern Health Office of Research & Ethics
Position	Manager
Telephone	(03) 9895 3398
Email	ethics@easternhealth.org.au

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Consent Form

Box Hill Hospital

Title	The Effect of Tirzepatide versus Dulaglutide on Major Adverse Cardiovascular Events in Patients with Type 2 Diabetes
Short Title	SURPASS-CVOT
Protocol Number	I8F-MC-GPGN
Study Sponsor	Eli Lilly Australia Pty Ltd
Principal Investigator	A/Prof Richard Simpson
Location	Box Hill Hospital – Arnold Street, Box Hill VIC 3128, Australia

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand, and I have had time to think about it.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to Eastern Health concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and to follow the study procedures and provide necessary information to the doctor, nurses, or other staff members, as requested.

I understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please print) _____

Signature _____ Date _____

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the study, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the study team that is qualified by education, qualifications and training must provide the explanation of, and information concerning, the study.

Declaration by Impartial Witness* (if applicable; use this section only if required
I declare that I have been present when the research was explained to the above-named participant and to the best of my observation and belief was understood and the consent freely given.

Name of Witness* to Informed Consent Process,

if applicable (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Note: All parties signing the consent section must date their own signature.

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Form for Withdrawal of Participation

Title	The Effect of Tirzepatide versus Dulaglutide on Major Adverse Cardiovascular Events in Patients with Type 2 Diabetes
Short Title	SURPASS-CVOT
Protocol Number	I8F-MC-GPGN
Study Sponsor	Eli Lilly Australia Pty Ltd
Principal Investigator	A/Prof Richard Simpson
Location	Box Hill Hospital – Arnold Street, Box Hill VIC 3128, Australia

Declaration by Participant

I wish to withdraw from participation in the above study and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with Eastern Health.

Name of Participant (please print) _____

Signature _____ Date _____

In the event that the participant's decision to withdraw is communicated verbally, the Study Doctor/Senior Researcher will need to provide a description of the circumstances below.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the study and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the study team must provide the explanation of and information concerning withdrawal from the study.

Note: All parties signing the consent section must date their own signature.

Attachment 1. I8F-MC-GPGN Study Procedures

Schedule of Activities: Screening through 24 Weeks (Visit 14)

	Screening	**Dose Escalation Period**												
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Week of Treatment	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**
Come in Fasting		**X**												
Study staff may contact you by phone rather than have you come into the study site			**X**		**X**		**X**		**X**		**X**		**X**	
Informed consent	X													
Receive study drug		X		X		X		X		X		X		X
Bring study drugs to study site				X		X		X		X		X		X
Medical history and physical examination	X													
Your doctor will ask what medications you are taking and how you are feeling	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pulse rate and blood pressure	X	X		X		X		X		X		X		X
ECG		X												
Height, weight, and waist circumference (height only at screening)	X	X						X						X
Eye exam	X													
Pregnancy test for women of childbearing potential (blood test at screening, urine test at Visit 2)[a]	X	X												
Approximate blood draw amount in mL[b]	17	40						8						8
You will provide a urine sample		X												
Receive injection training at this visit and as required[c]		X												
Answer questionnaires		X												X

Abbreviation: ECG = electrocardiogram.

[a] You may have more urine pregnancy tests during the study. If required per local regulations and/or institutional guidelines, pregnancy testing can also occur at other times during the study treatment period.

[b] If required, additional blood samples or information may be collected.

[c] You will be observed injecting the first dose of study medication (the entire solution in the single dose pen) under the supervision of the investigator site. After Visit 2, injection instructions will be reviewed as needed.

Schedule of Activities: 9 Months to Final Visit

	Maintenance Period																Extended Maintenance Period				Early Termination		Final Visit
Visit	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**EVa (31, 35, etc)**	**EVb (32, 36, etc)**	**EVc (33, 37, etc)**	**EVd (34, 38, etc)**	**ETV**	**Post-ETV (60)**	**99**
Study Month	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36**	**39**	**42**	**45**	**48**	**51**	**54**	**(+3)**	**(+6)**	**(+9)**	**(+12)**	**-**	**(+1)**	**-**
Come in Fasting		**X**				**X**								**X**							**X**		**X**
Receive study drug	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Bring study drugs to study site	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Physical examination																					X		X
Your doctor will ask what medications you are taking and/or how you are feeling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pulse rate and blood pressure		X		X		X		X		X		X		X		X		X		X	X		X
Height, weight, and waist circumference (height only at ETV and final visit)		X				X				X				X				X			X		X
You will provide a urine sample		X				X				X				X				X			X		X
Approximate blood draw amount in mL[a]		16				38				16				16				16			40		40
Answer questionnaires						X															X		X

	Maintenance Period																Extended Maintenance Period				Early Termination		Final Visit
Visit	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**EVa (31, 35, etc)**	**EVb (32, 36, etc)**	**EVc (33, 37, etc)**	**EVd (34, 38, etc)**	**ETV**	**Post-ETV (60)**	**99**
Study Month	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36**	**39**	**42**	**45**	**48**	**51**	**54**	**(+3)**	**(+6)**	**(+9)**	**(+12)**	**-**	**(+1)**	**-**
Come in Fasting		**X**				**X**								**X**							**X**		**X**
Urine pregnancy test for women of childbearing																					X[b]		X[b]

Abbreviations: ETV = early termination visit; EV = extended maintenance visit.

[a] If required, additional blood samples or information may be collected.

[b] You will have a urine pregnancy test at the time you permanently stop taking the study drug.