Study Participant Information and Consent Form And Authorization to Use and Disclose Protected Health Information

Sponsor / Study Title:	**Eli Lilly and Company / "The Effect of Tirzepatide versus Dulaglutide on Major Adverse Cardiovascular Events in Patients with Type 2 Diabetes (SURPASS-CVOT)"**
Protocol Number:	**I8F-MC-GPGN(b)**
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Introduction

You are being asked to voluntarily be in a research study of an experimental drug known as tirzepatide. Eli Lilly and Company and its representatives ("sponsor") are sponsoring this study and are paying the study doctor and/or the study site for their work in this study.

The purpose of this form is to help you decide if you want to be in this study.

Please read this form carefully. It may contain words that you do not understand. Please ask the study doctor or study nurse to explain any words or information that you do not clearly understand. You may take home an unsigned copy of this form to think about or discuss with family or friends before making your decision. If you sign and date this form, you are giving your permission (or consent) to be a part of this study. You can agree to take part in this study and change your mind later.

If any important new information is found during this study that may affect your wanting to continue to be part of this study, you will be told about it right away.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Confidentiality of Study 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 study drug 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.

Why is this study being done?

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 in preventing cardiovascular (heart and blood vessel) events in participants with type 2 diabetes and a higher risk of cardiovascular events (you may benefit from drugs that either do not increase this risk or prevent new serious cardiovascular complications).

This study is being done to see how safe an investigational drug is and how well it will work to help people with cardiovascular events in participants with type 2 diabetes. “Investigational” means that the study drug being tested has not been approved for routine clinical use or for the use described in this study by the United States Food and Drug Administration (FDA). The FDA is allowing the use of this study drug for research only.

How many people will take part in the study?

Approximately 12,500 study participants will be enrolled in this study.

What will happen during the study?

You will be asked to:

- Sign and date this consent form.
- Give your health history. The study staff will review your medical history and test results to see if you can be part of this study.
- Tell the study staff if you take any over-the-counter or prescription drugs, vitamins, or herbs.

The study staff will discuss what is required for you to be part of this study.

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 hospitalized due to heart failure within 2 months prior to screening.
- You have had a heart attack within 60 days before screening, or had bypass heart surgery within 5 years before 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 (inflammation of the liver).
- 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 may need to have some exams or tests done to find out if you are a candidate to begin the investigational drug. Some of these tests may be done even if you do not join the study as part of your normal care. If these exams or tests have been done recently, they may not need to be repeated.

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

You will be randomized (assigned by chance, like the flip of a coin) to receive either an increasing dose of tirzepatide (up to 15 mg) or dulaglutide (1.5 mg). You have an equal chance of receiving either study drug. Neither you nor the study doctor will know which study drug you are taking. However, your study doctor can find out which study drug you were given if there is an emergency.

You will inject the study drug subcutaneously (under the skin) 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 diarrhea. If you have these side effects, you will remain on the highest dose you can tolerate until Visit 16. In order to maximize study 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 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 study 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 1,615 participants experience a certain cardiovascular event (including heart attack, stroke, or cardiovascular event).

Even if you stop taking 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 study staff will stay in contact with you by phone until the end of the study.

You will:

- use the study drug only as instructed by the study staff
- return any unused study drug and containers after each visit, or as instructed by the study staff
- give yourself the study drug by subcutaneous injection (under the skin)

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.

It is important that you are completely truthful with the study staff about your health history. It may be harmful to you or to other people who may take the study drug if you are not truthful with the study staff. You should not take part in this study if you do not meet all requirements.

The duration of your participation depends on how long it takes for 1,615 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 study 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.

Please review the table below. This will give you information about what will happen at each specific visit and how often the procedures will happen.

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 Study 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 study 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 measurement of your heart's rhythm.

[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 drug (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 study 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
Urine pregnancy test for women of childbearing potential																					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.

Are samples being collected?

Please review the information below. This explains what samples are being collected, how they will be used, and how long they will be stored. Additional samples may be required to repeat a test if needed. The samples and any data generated from the sample can only be linked back to the study participant by the study staff.

General Information Regarding Sample Collection

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 sample(s) 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.

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 study staff will contact you. The study doctor may be required by law to report the result of these tests to the local health authority.

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 drugs. For this reason, looking at DNA can sometimes help explain why people with a disease respond differently to the same drugs. For example, some people taking this study drug may respond well. Others may have little or no response, or have side effects.

Researchers may study your DNA to learn how the study drug 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.

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.

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.

What if I lose contact during the study?

If you are not able to attend a planned study visit or maintain telephone contact, the study doctor or study 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 study 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 study 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 study 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 study staff.

What side effects or risks can I expect from being in the study?

There may be risks to you if you are in this study.

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 participants were considered overweight or obese. The Sponsor has reviewed safety information from these studies.

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

Very Common (10 or more out of 100 participants)	• Feeling sick to the stomach • Loose or frequent stools • Throwing up, vomiting • Loss of appetite
Common (1 or more out of 100 participants)	• 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 participants)	• Feeling full quickly when eating

Cases of pancreatitis have been reported in people 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 hospitalization 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 diarrhea 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 participants 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 participants 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 HR 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 (hypoglycemia). While taking tirzepatide, you may be more likely to have low blood sugar if you are also taking insulin or an insulin secretagogue (such as sulfonylurea). 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 people taking other GLP-1 medicines and may be a potential side effect with tirzepatide. Tirzepatide should not be given to participants 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 study 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:

Like all drugs, this study drug can cause side effects, although not everybody gets them.

<u>Severe side effects</u>

Rare (may affect up to 1 in 1000 people)	• Severe allergic reactions (anaphylactic reactions, angioedema). You should see a doctor immediately if you experience symptoms such as: ○ Rashes ○ Itching ○ Rapid swelling of the tissues of the neck, face, mouth or throat ○ Hives ○ Difficulty 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)	• Nausea (feeling sick) • Vomiting (being sick) • Diarrhea • Abdominal (stomach) pain These side effects are usually not severe. They are most common when first starting dulaglutide, but decrease over time in most people. • Hypoglycemia (low blood sugar) is very common when dulaglutide 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.
Common (may affect up to 1 in 10 people)	• Hypoglycemia is common when dulaglutide 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 study 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 (may affect up to 1 in 100 people)	• Injection site reactions (such as rash or redness) • Allergic reactions (hypersensitivity) (for example, swelling, raised itchy skin rash [hives]) • Dehydration, often associated with nausea, vomiting, and/or diarrhea • Gallstones • Inflamed gallbladder

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

Cases of pancreatitis have been reported in healthy participants and people with type 2 diabetes who have received dulaglutide. 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 hospitalization and even death. Dulaglutide has not been evaluated in people with a prior history of pancreatitis. Cases of pancreatic cancer have been reported in people with type 2 diabetes who have received dulaglutide. The effects of dulaglutide on this cancer are not known.

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

Symptoms of nausea, vomiting, and diarrhea 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 people with type 2 diabetes with cardiovascular disease or multiple cardiovascular risk factors, diabetic retinopathy complications, which cause issues with the eyes, occurred in people treated with dulaglutide 1.5 mg (1.9%) and placebo (1.5%). The proportion of people with these complications was larger among people 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 study doctor will 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 people taking dulaglutide. 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 with or without other anti-diabetic drugs, your blood sugar could be lowered too much (hypoglycemia). The risk of hypoglycemia is increased when dulaglutide is used in combination with insulin secretagogues (such as sulfonylureas) or insulin. You may require a lower dose of sulfonylurea or insulin to reduce the risk of hypoglycemia 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 participant in a dulaglutide study. This participant's calcitonin (a hormone in the blood that is high with this type of cancer) value was high prior to getting dulaglutide study drug, suggesting the tumor was present before the study. The effects of dulaglutide on this cancer are not known. Since you are participating in a long-term study with dulaglutide, your calcitonin levels will be measured to detect any potential medullary thyroid disease.

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

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

Dulaglutide has not been tested in pregnant women. Studies in animals have shown problems with reproduction. You should not take dulaglutide 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.

Procedure Risks

Blood Tests

Needle punctures for blood draws may cause bleeding, bruising, discomfort, infections and/or pain where you had the blood drawn. You may also feel dizzy or faint.

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.

Questionnaires

Some people feel uncomfortable when answering questions about the quality of their life. Though it is always better to have fully completed questionnaires, you do not need to answer any questions that make you feel uncomfortable.

Please talk to the study doctor or study staff about any questions or concerns that you may have about the procedures required for this study.

What are the Reproductive Risks?

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 study doctor about the types of birth control that are best for you and your partner. Tell your study doctor right away if you become pregnant or think you are pregnant. The study doctor will want to follow your pregnancy and record its outcome.

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 study doctor about the types of birth control that might be best for you and your partner. Tell the study doctor right away if your partner becomes pregnant or thinks she may be pregnant. The study doctor will want your partner’s permission to follow her pregnancy and record its outcome. Also, you should not donate semen/sperm during your participation in the study and for 3 months after the last dose of the study drug.

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.

Some methods of birth control may be less effective. Please discuss birth control methods with your study doctor.

There may also be unknown risks to your embryo, fetus, or nursing child.

Other Risks

In addition to the side effects already described, tirzepatide and dulaglutide, and the study procedures may have other unknown risks.

There may be unknown risks of possible harmful interaction with other medication you may be taking.

You should not give the study drug to other people and should keep it out of the reach of small children.

Are there benefits to taking part in the study?

You may or may not receive any benefit from being in this study. If you take part in this study, other people with type 2 diabetes with established cardiovascular disease may be helped.

Information obtained from this study will also benefit the sponsor of the study and may benefit study participants in the future. You may receive information from physical examinations, laboratory tests, or other testing that is done in this study, but these tests may not have any impact on your health.

What other choices do I have if I do not take part in this study?

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.

What happens if I want to stop the study?

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

Your participation also may be stopped by the study doctor or sponsor for any reason without your consent. If this happens, it might be due to a bad reaction you have to tirzepatide or dulaglutide or new information about tirzepatide's or dulaglutide's safety or effectiveness.

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

What are the costs of taking part in this study?

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

Greenphire Travel Reimbursement program is providing payment for inconvenience fees and travel reimbursement. You are invited to voluntarily take part in an optional program to reimburse you for your study inconvenience fees and travel expenses. You do not have to

participate, or you can also decide to stop participating at any time. Greenphire is also offering Lyft transportation services. Please speak with the study staff for more information.>

You will be provided a fixed amount of $50 per study visit for inconvenience fees related to time spent for lost wages and burden of the study for the following visits: V4, V6, V8, V10, V12, V15, V17-19, V21-V23, V25-V27, V29-V30, and if applicable, Extended Maintenance Visit A (EVa), Extended Maintenance Visit C (EVc), Extended Maintenance Visit D (EVd), and any unscheduled visits performed in accordance with the protocol.

You will be provided a fixed amount of $75 per study visit for inconvenience fees related to time spent for lost wages and burden of the study for the following visits: V1, dilated fundoscopic exam, V2, V14, V16, V20, V24, V28, V99, and if applicable, Early Termination Visit (ETV) Extended Maintenance B (EVb), and any unscheduled visits performed in accordance with the protocol.

You will be provided a fixed amount of $25 per study visit for inconvenience fees related to time spent for lost wages and burden of the study for the following visit, if applicable: Post-Early Termination Visit (Post-ETV).

You will be provided a fixed rate of $25 per telephone “visit” for the following visits: V3, V5, V7, V9, V11, and V13.

You may be reimbursed a fixed amount of $75 per dilated fundoscopic exam performed in accordance with the protocol for caregiver inconvenience related to time spent for lost wages and burden of the study.

You will also be provided a fixed amount of $0.24/mile starting at mile 1 round-trip per study visit when public transportation is not being paid. This amount applies to all visits conducted in accordance with the protocol.

You may be reimbursed actual expenses for all study visits completed on the items indicated below:

- Transportation will be reimbursed at least the minimum standard IRS mileage rate for medical transportation to cover transportation from your home address to the nearest study treatment center at time of enrollment. The IRS mileage rate may change periodically.
- Public transportation (taxis, bus, train, subway). When mileage is NOT being paid, you will receive up to $100. You will be reimbursed the actual amount up to the maximum amount per round trip visit. Car rental is not included in this coverage. Receipts are required.
- Parking fees and tolls, if applicable. There is a $50 maximum limit per visit. You will be reimbursed the actual amount up to the maximum amount. Parking fees will not be reimbursed if the cost is covered by the site. Receipts are required if applicable/available.
- Meal reimbursement will be provided for V2, V16, V20, V28, V99, and if applicable, ETV up to $25 per meal.

Note: The IRS requires that compensation (not documented by receipts or other tracking methods) greater than or equal to $600 be reported to the IRS as required by law. This IRS reporting will require you to provide your full Social Security Number. Refer to http://www.irs.gov/pub/irs-pdf/i1099msc.pdf. for full details on the information that is included on the IRS Form 1099-MISC.

If you do not finish the study, you will be reimbursed for the part of the study that you did complete. However, your expenses could be more than the amount you are reimbursed.

You will be paid after each completed visit.

More information about reimbursement is in the Study Participant Reimbursement Information Sheet.

What happens if I am injured because I took part in this study?

If you become ill or injured while you are in the study, please seek medical help right away. You should inform the healthcare professional treating you that you are participating in this study. If you tell the study staff that you think you have been injured, then they will help you get the care you need.

If you follow the directions of the study doctor and study staff, the sponsor will pay the medical expenses for the treatment of a physical injury because of a properly given drug or procedures. By signing and dating this document, you will not lose any of your legal rights or release anyone involved in the research from responsibility for mistakes.

To pay medical expenses, the sponsor will need to know some information about you like your name, date of birth, and Medicare Beneficiary Identifier (MBI). This is because the sponsor has to check to see if you receive Medicare and if you do, report the payment it makes to Medicare.

Whom to contact about this study?

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the study doctor at the telephone number listed on the first page of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research participants. If you have any questions about your rights as a research participant, and/or concerns or complaints regarding this research study, contact**:**

- By mail:
  Study Subject Adviser
  Advarra IRB
  6940 Columbia Gateway Drive, Suite 110
  Columbia, MD 21046
- or call **toll free**: 877-992-4724
- or by **email**: adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: Pro00039651.

Will my medical information be kept private?

The study doctor and study staff will handle your personal health information in a confidential manner.

By signing and dating this document for this study, you give permission ("authorization") for the uses and disclosures of your personal health information in the following ways.

- Your original medical records (which may contain your full name or other information that may directly identify you) may be shared with or viewed by to ensure the quality of the study conduct and study data:
    - The sponsor of the study and its representatives "sponsor",
    - the regulatory authorities in this country (such as the FDA) and in other countries, and
    - the ethical review board overseeing this study.
- Your study data (information collected for the study which only identifies you by a code and not your full name or other information that may directly identify you) may be shared with or viewed by:
    - the sponsor and their business partners (including those in other countries),
        - When the sponsor shares any data outside of this country, the sponsor will respect the terms of this data privacy statement even if other countries may have privacy laws that do not provide the same protections
        - The sponsor will only share your study data with their business partners, only if they need the information as a part of this work with the sponsor. The business partners must sign a contract that requires it to protect your study data in the same way as the sponsor.
    - the regulatory authorities in this country and in other countries,
    - the ethical review board overseeing this study, and
    - the doctors at other institutions participating in the study.
- The sponsor will use the study data:
    - to support the study purposes described in the consent document,
    - to determine how safe or effective any of the drugs or treatments 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 directly identify you may be published.

Your personal health information may no longer be protected under the Health Insurance Portability and Accountability Act (HIPAA) privacy rule once it is disclosed by your study doctor to these other parties.

You have the right to see and copy your personal health information related to the research study. However, you may not be able to review some of the study data until after the study has been completed to ensure the scientific integrity of the study.

Your authorization for the uses and disclosures of your personal health information does not have an expiration date. In California and any other state that requires an expiration date, this authorization will expire 50 years after you sign and date this document.

You may cancel your authorization for the uses and disclosures of your personal health information at any time by providing written notice to the study doctor at the address listed on the first page of this form. If you cancel your authorization:

- The study doctor and study staff will only use or disclose some of your personal health information if it is needed to confirm the accuracy of the study data.
- The sponsor will still use study data that was collected before you cancelled your authorization.
- You will no longer be able to participate in the study.

Statement of Authorization

I have read this form and its contents were explained. My questions have been answered. I voluntarily agree to allow study staff to collect, use and share my health data as specified in this form. I will receive a signed and dated copy of this form for my records. I am not giving up any of my legal rights by signing and dating this form.

FOR STUDY PARTICIPANT TO COMPLETE

Signature of Study Participant	Date (Study Participant must personally date)

Study Participant Name (print or type)

FOR INDIVIDUAL CONDUCTING AUTHORIZATION DISCUSSION TO COMPLETE

Name of Individual Conducting Authorization Discussion (print or type)

Signature of Individual Conducting Authorization Discussion

Date
(Individual Conducting Authorization Discussion must personally date)

Study Participant Information and Consent Form Signature Page

To become a part of this study, and to authorize use and disclosure of your personal health information, you must sign and date this page.

Only sign and date this consent after:

- You have read all of the information in this Study Participant Information and Consent Form, and you have had time to think about it.
- All of your questions have been answered to your satisfaction.

You voluntarily agree to be part of this research study, and to do the following:

- to follow the study procedures, and
- to provide necessary information to the study doctor, study nurses, or other study staff members, as requested, and
- allow the study doctor and the sponsor to use and disclose your personal health information as described in this document

You may freely choose to stop being a part of this study at any time. You will receive a copy of this signed and dated Study Participant Information and Consent Form to keep.

FOR STUDY PARTICIPANT TO COMPLETE

Signature of Study Participant	Date (Study Participant must personally date)

Study Participant Name (print or type)

FOR INDIVIDUAL CONDUCTING INFORMED CONSENT DISCUSSION TO COMPLETE

I have explained the study (such as the purpose, risks, benefits and the procedures) to the study participant before the study participant voluntarily agreed to participate.

Name of Individual Conducting Informed Consent Discussion (print or type)

Signature of Individual Conducting Informed Consent Discussion	Date (Individual Conducting Informed Consent Discussion must personally date)