The Effect of Tirzepatide versus Dulaglutide on Major Adverse Cardiovascular Events in Patients with Type 2 Diabetes (SURPASS-CVOT)

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This study has been transitioned to CTIS with ID 2023-507846-96-00 check the CTIS register for the current data. The main reason for conducting this study is to help in answering the following research question:• How tirzepatide compares to...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Diabetic complications
Study type	Interventional

Summary

ID

NL-OMON52730

Source
ToetsingOnline

Brief title
I8F-MC-GPGN (SURPASS-CVOT)

Condition

- Diabetic complications

Synonym
'Adverse Events relating to the Heart and Blood Vessels in Patients with Type 2 Diabetes' and 'Cardiovascular Events in Patients with Type 2 Diabetes'

Research involving
Human

Sponsors and support

Primary sponsor: Eli Lilly
Source(s) of monetary or material Support: Eli Lilly and Company

Intervention

Keyword: Cardiovascular, Dulaglutide, Tirzepatide, Type 2 Diabetes

Outcome measures

Primary outcome

Time to first occurrence of a component event of a MACE-3.

Secondary outcome

Key Secondary efficacy measures are:

• Time to death due to any cause;

• Time to CV death;

• Time to first occurrence of MI;

• Time to first occurrence of stroke.

• Time to first occurrence of the expanded composite CV outcome, defined as either CV death, MI, stroke, coronary revascularisation, hospitalisation for unstable angina

• Cumulative number of CV deaths and total (first and recurrent) HF events requiring hospitalization and/or urgent HF visits.

Additional secondary measures are:

• Proportion of patients with more than 10% weight loss from screening after 36 months;

• Change from baseline in:

- weight, BMI, and waist circumference

- HbA1c

- urinary albumin to creatinine ratio

- blood lipids: total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides;

• Time to first occurrence of:

- coronary, carotid, or peripheral revascularisations, individually and as composite

- hospitalisation due to unstable angina

- composite endpoint of new or worsening nephropath;

• Cumulative number of primary composite events of CV death and total (first and recurrent) MI and/or stroke;

• Maximally tolerated tirzepatide dose will be measured based on:

• Incidence of TEAEs and permanent discontinuation of study drug due to AEs

• Incidence of:

- pancreatitis

- severe gastrointestinal events

- any malignancy (including medullary and papillary thyroid cancers)

- severe hypoglycemic events

- Immune-mediated reactions including serious allergic and hypersensitivity reactions

- hepatobiliary events (eg, acute cholecystitis, acute cholelithiasis and drug-induced liver injury)

- acute renal failure or exacerbation of chronic renal failure

- diabetic retinopathy complications

- supraventricular arrhythmias and cardiac conduction disorders

• Mean change from baseline:

- blood pressure and pulse rate

- lipase

- pancreatic amylase

- calcitonin

- eGFR.

The effects of add-on therapy with up to 15 mg tirzepatide compared to

dulaglutide 1.5 mg will be measured based on:

• Change of antihyperglycemic drugs

• Patient-reported outcome

- APPADL

- IW-SP

- EQ-5D-5L

• Time to initiation of insulin of more than 3 months duration for those

patients not treated with insulin at study start

• eGFR from Cystatin-C.

Study description

Background summary

Tirzepatide is an investigational medicine called a dual agonist of
glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1

(GLP-1) receptors. It helps increase the release of insulin in the body, which in turn lowers the levels of glucose in the body and its use could result in substantial weight loss. GLP-1 receptor only agonists, such as dulaglutide, have been shown to protect the cardiovascular system in the body, and to reduce unwanted adverse cardiovascular events.

Tirzepatide could exceed the efficacy of most currently available type 2 diabetes medications in lowering glucose while possibly preventing cardiovascular events in participants with type 2 diabetes. This study is planned to compare tirzepatide to the currently available medication dulaglutide and to evaluate the cardiovascular safety and protection of tirzepatide in patients with type 2 diabetes.

Study objective

This study has been transitioned to CTIS with ID 2023-507846-96-00 check the CTIS register for the current data.

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

• How tirzepatide compares to dulaglutide 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).

Study design

SURPASS-CVOT is a Phase 3, event-driven, multi-centre, international, randomised, double-blind, active comparator, parallel-group study. This study will assess the effect of once weekly (QW) tirzepatide, on MACE-3, compared to QW dulaglutide, when added to the standard of care (SoC) in patients with Type 2 Diabetes Mellitus (T2DM) with established Cardiovascular Disease (CVD) and elevated risk for Major Adverse Cardiovascular Event (MACE).

In addition to study drug, all patients should receive standard of care for their diabetes and CVD.

The study comparison is between tirzepatide and dulaglutide. Assignment to tirzepatide or dulaglutide will be randomly allocated in a 1:1 ratio. Randomisation will be stratified by country of enrolment and SGLT-2i use.

Tirzepatide will be administered once weekly with doses being escalated at 4-weekly intervals from the starting dose to a maximum dose defined in the study protocol, or to the highest maintenance dose tolerated by the patient. The dose of dulaglutide will be initiated and maintained at 1.5 mg QW. To

maintain blinding, a sham escalation of dulaglutide will be employed.

In order to reduce risk of hypoglycaemia, specific, individually tailored adjustments of the respective anti-hyperglycaemic medications should be considered during the entire study. At Visit 2, with the initiation of study drug, dose adjustments to the concomitant glucose lowering medications will be recommended per the protocol.

During the dose escalation period, if a telephone visit is deemed necessary to support patient compliance, this is allowable at the discretion of the investigator site personnel. Optional telephone visits can be performed approximately 2 weeks after starting study drug and after each dose increase.

To optimise the number of patients who achieve the maximum escalation, both tirzepatide and dulaglutide patients who do not reach the maximum escalation during the initial dose escalation period will undergo a second dose escalation.

Patients will be followed for CV outcomes and other measures every 4 weeks for the first 24 weeks and then followed approximately every 3 months thereafter. The primary analysis of this study is an intention-to-treat (ITT) analysis; therefore, every randomised patient will be followed until the patient*s *end-of-follow-up,* regardless of compliance with study drug and adherence to study visit schedule.

Approximately 12,500 patients will be enrolled at approximately 650 sites globally.

Patients will be followed until at least 1615 patients experience a primary endpoint event, centrally adjudicated as such. This is projected to occur after an average of approximately 48 months of follow-up. The trial may be stopped earlier on the basis of an Independent Data Monitoring Committee (IDMC) safety review or for efficacy at the interim analysis.

A study duration of approximately 54 months is planned, but duration depends on accrual of the requisite number of patients experiencing at least 1 component of the primary endpoint. Consequently, additional visits may be required beyond the planned duration. These additional visits, similar to visits during the maintenance period, will occur every 3 months.

Approximately 3 months prior to the anticipated date of attaining 1615 events, a study close-out period will be declared. During the study close-out period, a final visit will be planned for each patient.

Intervention

Tirzepatide will be administered once weekly with doses being escalated at 4-weekly intervals from the starting dose to a maximum dose defined in the

study protocol, or to the highest maintenance dose tolerated by the patient. The dose of dulaglutide will be initiated and maintained at 1.5 mg QW. To maintain blinding, a sham escalation of dulaglutide will be employed.

Study burden and risks

The safety characteristics of tirzepatide are similar to that of dulaglutide. The most common Adverse Events (AEs) were nausea, vomiting, and diarrhoea. In general, these events are mild or moderate, with few severe events, and transient. The highest previously tested tirzepatide dose was associated with more gastro-intestinal (GI) AEs after a relatively short dose escalation period. However, it is suggested that slower dose escalation and smaller dose increments might improve tolerability.

Previous studies indicate that the potential risks/AEs with tirzepatide are consistent with GLP-1 Receptor Agonists (RAs). The risks also include the development of potential compound-specific anti-drug antibodies, similar to other protein-based therapies. No apparent GIP RA effects have been identified that would suggest additional or differential safety risks.

In clinical trials completed to date, dulaglutide has exhibited the expected effect on insulin secretion and resulting in significant reductions in HbA1c. Dulaglutide administration in patients with T2DM has been associated with reductions in body weight. The most common AEs reported in patients administered dulaglutide are those related to the GI organ class, including nausea and vomiting

Various anti-hyperglycaemic background medications will be used throughout the study. Some agents, like sulfonylureas (SUs) and insulins, may be associated with occurrence of hypoglycaemia. This potential risk will be monitored throughout the study and measures will be implemented to reduce the risk of hypoglycaemia, including initial dose reduction and/or discontinuation of these agents and frequent dose adjustment at the investigator*s discretion.

Normally patients with T2DM may visit their doctor once every three to six months to monitor their disease. Doctors would normally ask questions to check their physical, mental and nutritional health. They may perform a physical exam, check their weight, blood pressure, and heart rate. The visits that are involved in this study are more frequent and are in addition to these normal health checks. However, patients may benefit from frequent expert medical care for an approximately 54-month period.

There are risks that may be associated with the tests performed on the study such as blood tests, ECGs, eye exams and from injection needle punctures from administering the study drugs. Clinically routine monitoring and measures will be implemented at the investigator*s discretion, to reduce the risk of these occurring or to provide the appropriate care to patients that may experience

them.

Contacts

Public
Eli Lilly

Eastgate Business Park, Little Island 11 Eastgate Road, Island House
Cork T45 KD39
IE
Scientific
Eli Lilly

Eastgate Business Park, Little Island 11 Eastgate Road, Island House
Cork T45 KD39
IE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

[1] Men or women at least 40 years old with a diagnosis of T2DM (WHO 2019).
[2] Established CVD, including at least 1 of the following (a-c):
a. Coronary artery disease (CAD) with EITHER of the following:
- Documented history of spontaneous MI
- >=50% stenosis in 1 or more major coronary arteries, determined by invasive angiography
- >=50% stenosis in 2 or more major coronary arteries, determined by computed tomography coronary angiography (CTCA), or
- History of surgical or percutaneous coronary revascularization procedure;

b. Cerebrovascular disease - ANY of the following:
- Documented history of ischemic stroke
- Carotid arterial disease with >=50% stenosis, documented by carotid ultrasound, magnetic resonance imaging (MRI), or angiography
- Carotid stenting or surgical revascularization;
c. Peripheral arterial disease with EITHER of the following:
- Intermittent claudication and ankle-brachial index <0.9
- Prior nontraumatic amputation or peripheral vascular procedure (e.g., stenting or surgical revascularization), due to peripheral arterial ischemia.
[3] HbA1c >=7% (>=53 mmol/mol) and <=10.5% (<=91.3 mmol/mol) based on central laboratory assessment at screening.
[4] Body mass index (BMI) >=25 kg/m2.
[5] At the time of signing the informed consent: Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical trials.
[6] In the investigator*s opinion, patients are well motivated, capable, and willing to learn how to self-inject treatment (tirzepatide or dulaglutide), as required for this protocol (visually impaired persons and/or persons with physical limitations who are not able to perform the injections must have the assistance of an individual trained to inject the study drug).
[7] Patients are capable of giving signed informed consent.

Exclusion criteria

[8] Have type 1 diabetes mellitus.
[9] Have uncontrolled diabetes requiring immediate therapy (such as diabetic ketoacidosis) at screening or randomization, in the judgment of the physician.
[10] Have had 1 or more events of severe hypoglycaemia and/or 1 or more events of hypoglycaemia unawareness within 6 months prior to screening.
[11] Are currently planning treatment for diabetic retinopathy and/or macular oedema.
[12] Have been hospitalized for CHF within 2 months prior to screening.
[13] Have chronic New York Heart Association Functional Classification IV CHF.
[14] Are currently planning a coronary, carotid, or peripheral artery revascularization.
[15] Had chronic or acute pancreatitis any time prior to screening, irrespective of aetiology.
[16] Have a known clinically significant gastric emptying abnormality such as severe gastroparesis or gastric outlet obstruction, or have undergone or currently planning any gastric bypass (bariatric) surgery or restrictive bariatric surgery
[17] Have acute or chronic hepatitis, signs or symptoms of any other liver disease, or an alanine aminotransferase (ALT) level >=3X the upper limit of normal (ULN) for the reference range, as determined by the central laboratory.
[18] Have known chronic severe renal failure (defined as a known eGFR <15

mL/minute/1.73 m2) or are on chronic dialysis.
[19] Have evidence of a significant, uncontrolled endocrine abnormality (eg, thyrotoxicosis or adrenal crises).
[20] Have a family or personal history of multiple endocrine neoplasia type 2 (MEN2) or familial medullary thyroid carcinoma (MTC) or personal history of nonfamilial MTC.
[21] Have a serum calcitonin level at screening of: (based on central laboratory results)
- >=20 ng/L at Visit 1, if eGFR >=60 mL/min/1.73 m2, or
- >=35 ng/L at Visit 1, if eGFR <60 mL/min/1.73 m2.
[22] Have a history of an active or untreated malignancy or are in remission from a clinically significant malignancy for less than 5 years. An exception for this criterion is basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer.
[23] Have a history of any other condition (such as known drug or alcohol abuse or psychiatric disorder) that, in the opinion of the investigator, may preclude the patient from following and completing the protocol.
[24] Have had a transplanted organ (corneal transplants [keratoplasty] allowed) or awaiting an organ transplant.
[25] Have any other condition (eg, hypersensitivity) that is a contraindication to any incretin or GLP-1 RAs.
[26] Have had an MI, percutaneous coronary revascularization procedure, ischemic stroke, carotid stenting or surgical revascularization, nontraumatic amputation, or peripheral vascular procedure (eg, stenting or surgical revascularization) less than 60 days prior to screening
[27] Have had coronary artery bypass graft surgery less than 5 years prior to Screening.
[37] Have had a blood transfusion or severe blood loss within 90 days prior to screening or have known haematological conditions that may interfere with HbA1c measurement.
[28] Treatment with GLP-1 RA or pramlintide, in a period of 3 months prior to Visit 1
[29] Discontinuation of GLP-1 RA or pramlintide, due to intolerability any time prior to Visit 1
[30] Exclusion Criterion [30] has been deleted.
[31] Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.
[32] Have participated within the last 30 days in a clinical trial involving an investigational product. If the previous investigational product has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed.
[33] Have previously completed or withdrawn from this study or randomized into any other study investigating tirzepatide.
[36] Any women who are pregnant or breastfeeding.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-10-2020
Enrollment:	336
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Tirzepatide
Generic name:	Tirzepatide
Product type:	Medicine
Brand name:	Trulicity
Generic name:	Dulaglutide
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	20-04-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO Date:	09-06-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-08-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-08-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-01-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-02-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-06-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-06-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-08-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-01-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	15-02-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-01-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-03-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-04-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2023-507846-96-00
EudraCT	EUCTR2019-002735-28-NL
CCMO	NL72286.091.20