A phase IV, randomized, double-blind, placebo-controlled, parallel-group trial to assess the effect of 12-week treatment with the glucagon-like peptide-1 receptor agonist (GLP-1RA) liraglutide or dipeptidyl peptidase-4 inhibitor (DPP-4i) sitagliptin on the cardiovascular, renal and gastrointestinal system in insulin-naïve patients with type 2 diabetes (T2DM).

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Overarching Aim: to detail the (mechanisms underlying the) actions of GLP-1RA and DPP-4i on the cardiovascular, renal and gastrointestinal system patients with T2DM. For the sake of clarity, we divide the study objectives into 3 parts:Primary...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Interventional

Summary

ID

NL-OMON41271

Source
ToetsingOnline

Brief title
SAFEGUARD, Pleiotropic effects of incretin based therapies

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
Type 2 Diabetes Mellitus

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: FP7/2007-2013 (EU) en Nederlandse Nierstichting,Novo Nordisk

Intervention

Keyword: Diabetes, DPP-4, GLP-1

Outcome measures

Primary outcome

Cardiovascular part: resting heart rate variability

Renal part: glomerular filtration rate.

Gastrointestinal part: fecal elastase-1.

Secondary outcome

Cardiovascular part:

- Blood pressure

- Heart rate

- Hemodynamic variables

- Autonomic nervous system (ANS) function

- Microvascular function

- Arterial stiffness

- Plasma lipid spectrum

- Glycemic variables

- Body anthropometrics and body fat content

Renal part:

- Renal plasma flow

- Renal tubular function

- Renal damage parameters

Gastrointestinal part:

- Pancreatic exocrine function/structure

- Plasma pancreatic enzymes

- Gallbladder motility

- Liver enzymes

- Hepatic function

- Hepatic steatosis

- Gastric emptying speed

Study description

Background summary

Currently published data on the effects and side effects of the new blood-glucose lowering incretin-based agents (glucagon like peptide-1 receptor agonists (GLP-1RA) and dipeptidyl peptidase-4 inhibitors (DPP-4i)) are primarily derived from large-scaled registration studies in patients with type

2 diabetes mellitus (T2DM). By definition these international, multi-center, randomized-controlled trials (RCTs) focus on glycemic control as a primary outcome. Already in these phase III trials, but increasingly so during the post-marketing period, incidental reports have suggested a possible association between the use of these agents and changes in cardiovascular parameters (increased heart rate), acute renal failure and pancreatitis. Indeed, GLP-1 receptors are present in most organ systems of the human body and consequently, pharmacological interventions enhancing GLP-1 activity may influence the functioning of these organs, in addition to their favorable effects on the endocrine pancreas. Currently, for most of the registered incretin-based compounds, large-scaled long-term outcome trials are underway, as required by the recently issued Federal Drug Administration (FDA) and European Medicines Agency (EMA) guidance. These trials may hopefully provide more clarity with respect to the possible causal relationship between the use of these drugs and fore-mentioned adverse events and the forthcoming clinical implications. However, the results of these trials may not become available before 2016. Conversely, to date, studies in humans detailing the effects on these organ systems, biological processes and underlying mechanisms, which could explain these associations, are lacking. Therefore, as part of the EU-FP7 program, the EMA has endorsed a project to study the pharmaco-epidemiological aspects of these potential side effects and the underlying mechanisms within the SAFEGUARD consortium. The present study is part of the SAFEGUARD Work Package 6, mechanistic studies (WP-6 leader: prof. M. Diamant).

Study objective

Overarching Aim: to detail the (mechanisms underlying the) actions of GLP-1RA and DPP-4i on the cardiovascular, renal and gastrointestinal system patients with T2DM.

For the sake of clarity, we divide the study objectives into 3 parts:

Primary objectives:
Cardiovascular part: to assess the acute effects of GLP-1RA and the long-term effects of both GLP-1RA and DPP-4i on resting heart rate variability.
Renal part: to assess the acute effects of GLP-1RA and the long-term effects of both GLP-1RA and DPP-4i on glomerular filtration rate.
Gastrointestinal part: to assess the long*term effect of GLP*1RA and DPP*4i on fecal elastase-1.

Secondary objectives:
Cardiovascular part: to measure the acute effects of GLP-1RA and the long-term effects of both GLP-1RA and DPP-4i on blood pressure, heart rate, hemodynamic variables, autonomic nervous system (ANS) function, microvascular function, arterial stiffness, plasma lipid spectrum, glycemic variables (all of the fore-mentioned variables will be assessed in the fasting and postprandial state), body anthropometrics and body fat content.

Renal part: to measure the acute effects of GLP-1RA and the long-term effects of both GLP-1RA and DPP-4i on renal plasma flow, renal tubular function and renal damage parameters.
Gastrointestinal part: to measure the acute effects of GLP-1RA on exocrine pancreatic function, and to measure the long*term effect of GLP*1RA and DPP*4i on different aspects of pancreatic exocrine function/structure, plasma pancreatic enzymes, gallbladder motility, liver enzymes, hepatic function, hepatic steatosis and gastric emptying speed.

Exploratory objectives:
To explore the long-term effects of GLP-1RA and DPP-4i on various relevant biomarkers.

For the pilot study preceding the trial, we have added the following objective:
To assess the changes following infusion of L-NMMA and the combination of infusion of exenatide and L-NMMA in GFR and ERPF in healthy male subjects. Also, we will validate 'contrast-enhanced ultrasound' which can potentially be used for measuring renal perfusion non-invasively.

Study design

A double-blind, randomized, placebo-controlled, 3-armed parallel-group trial to assess the effect of 12 weeks of treatment with the GLP-1RA liraglutide, the DPP-4i sitagliptin or matching placebos on the function of the cardiovascular, renal and gastrointestinal system in 60 T2DM patients. On the first day of the (consecutive) baseline examination days preceding the long-term intervention study, a sub study will be performed to assess the acute effects of GLP-1RA on the cardiovascular and renal systems. This will be a double-blind, randomized, placebo-controlled acute intervention with infusion of either the GLP-1RA exenatide or placebo. In a subset of 12 patients an acute MRI intervention will be performed during the baseline testing days of the main study (double blind, randomized, placebo-controlled, cross-over study with infusion of the GLP-1RA exenatide and placebo).

Cardiovascular parameters will be assessed using an oscillometric blood pressure device (Dinamap®; systolic, diastolic, mean blood pressure, heart rate), a continuous beat-to-beat blood pressure and electrocardiographic hemodynamic monitor (NexFin®; finger blood pressure (systolic, diastolic and mean), heart rate, stroke volume, cardiac output/-index/-contractility, systemic vascular resistance, rest heart rate variability, autonomic nervous system function/baroreceptor reflex sensitivity), capillary videomicroscopy and Laser Doppler (microvascular function) and applanation tonometry (SphygmoCor®; arterial stiffness). Blood will be sampled for the determination of plasma lipid spectrum (triglycerides, total-, HDL- and LDL-cholesterol), glycemic variables (glucose, HbA1c) and cardiovascular biomarkers (hsCRP, NT-proBNP). Body anthropometrics (body weight, height, body-mass index (BMI) and waist

circumference) and bio-impedance analysis (body fat content) will be performed. Renal parameters will be measured by the gold-standard inulin- and para-aminohippurate (PAH) clearance method, to quantify glomerular filtration rate (GFR) and effective renal plasma flow (ERPF), respectively. Fractional excretion of sodium and urea will be measured as marker of tubular function and urinary albumin/creatinine-ratio, NGAL, KIM-1 as markers of renal damage. Gastrointestinal parameters include exocrine pancreatic function assessments using validated laboratory methods for pancreatic exocrine enzyme (activity), such as fecal elastase-1, plasma lipase, amylase; as well as the 13C-mixed triglycerides breath test and secretin-enhanced Magnetic Resonance CholangioPancreatography (sMRCP). MRI and 1H-MRS will be used to measure pancreatic and hepatic structure and hepatic fat content, respectively. Abdominal ultrasound will be used to assess gallbladder emptying speed. Finally, liver enzymes (AST, ALT, GGT, ALP) and liver function (plasma albumin) will be measured in plasma samples and acetaminophen absorption kinetics will be measured to estimate gastric emptying speed.

Preceding this study, a pilot study will be performed in order to operationalize 4 methods (the inulin/PAH clearance, 13C-mixed triglycerides breath test, sMRCP and gallbladder ultrasoud). Healthy volunteers participating in this pilot study will undergo the same testing days as the main study, including the acute infusion study. Also, 'contrast enhanced ultrasound' will be performed during the renal test days to validate this technique. An extra testing day, which will not be performed in the main study, will be added to the pilot study to investigate the interaction between exenatide and L-NMMA on renal hemodynamics (GFR and ERPF). The long term intervention will not be used in the pilot study.

Intervention

Subjects will be randomized to either of the following arms:

Treatment arm 1: liraglutide 1.8mg s.c. once daily + sitagliptin placebo
Treatment arm 2: sitagliptin 100mg oral once daily + liraglutide placebo
Treatment arm 3: liraglutide placebo + sitagliptin placebo

Moreover, during the first baseline visit, an infusion with exenatide or placebo will be given.

Participants in the Acute MRI sub study (12 participants of the main study) will receive 2 additional MRI scans with placebo and exenatide.

Participants in the pilot-study will not be randomized for the long-term intervention, but will undergo the acute intervention with exenatide. Also, on an additional testing day both exenatide and L-NMMA will be administered.

Study burden and risks

We are well aware of the possible demand that may be imposed on the participants in this study. Participants of the pilot study will have to visit the clinical research unit for a total of 5 times (spread over 2 weeks), participants in the main study will travel 9 times, spread over 17 weeks (participants in the Acute MRI protocol: 11x). The duration of the visits ranges between 30 minutes and 10 hours. A total amount of 492.5 mL of blood will be drawn in the main study, and 404.5 mL in the pilot study. Some of the tests procedures can be perceived as demanding (i.e. the renal protocol, MRI-scans and fecal collection). However, we have gained ample experience with similarly demanding mechanistic drug intervention studies in T2DM patients. We have built in different ways to alleviate the burden for participants, including clear, repeated communication, frequent contacting and intensified (diabetes) care. During test-days, we provide meals and allow participants to read or watch TV/DVDs when possible.
The study examinations/tests are considered to be safe. No radiation or invasive procedures (besides intravenous peripheral catheters) are involved. During the study tests, some *diagnostic agents* need to be administered. Inulin, para-aminohippuric acid and stable-isotope labeled 13C-MTG are inert and have no side effects. For acetaminophen side-effects are very rare. Secretin can cause transient nausea and abdominal pain.
All medication used in this study has a marketing authorisation and is considered to be safe. Exenatide and liraglutide are known to cause mild and transient nausea, and sometimes vomiting. Sitagliptin can cause nasopharyngitis. As these agents have been used in previous studies at the VU University Medical Center there is ample experience. As in all drug intervention trials, in this study, we will closely monitor patients for adverse drug and study events during the follow-up visits and by telephone consultations (one, two and six weeks after the start of the study medication). Moreover, the research physicians are available for questions at all times.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Both genders
-Age between 35 and 75 years. Females must be post-menopausal (no menses >1 year).
-Type 2 diabetes (HbA1c 6.5-9% DCCT or 48-75 mmol/mol IFCC), who are being treated with a stable dose of oral antihyperglycemic agents (either metformin alone, SU alone or a combination of metformin and SU) for at least 3 months prior to inclusion.
-BMI 25 - 40 kg/m2
- Caucasian;For the preceding pilot-study:
- Males
- Age between 18 and 50 years
- BMI 25 * 40 kg/m2
- Caucasian

Exclusion criteria

- GFR < 60 mL/min/1.73m2
- Current / chronic use of the following medication: thiazolidinediones, GLP-1RA, DPP-4i, glucocorticoids, NSAIDs, insulin, antimicrobial agents, chemotherapeutics or immune suppressants. Subjects on diuretics will only be excluded when these drugs (e.g. hydrochlorothiazide) cannot be stopped for the duration of the study.
- History of or actual pancreatic disease or impaired pancreatic exocrine function (defined as needed use of pancreatic enzymes)
- Active liver disease or a 3-fold elevation of liver enzymes (AST / ALT) at screening
- History of or actual malignancy (with the exception of basal cell carcinoma)
- Current urinary tract infection and active nephritis

-Recent (<6 months) history of cardiovascular disease, including acute coronary syndrome, stroke, transient ischemic neurologic disorder or chronic heart failure (New York Heart Association grade II-IV)
- Current atrial fibrillation
- Chronic infectious or auto-immune disease
- Substance and/or alcohol abuse, defined as >4 units alcohol/day (because of risk of pancreatitis)
- History of allergy/hypersensitivity to GLP-1RA, DPP-4i, inulin, para-aminohippuric acid, acetaminophen, secretin, MRI contrast agent or latex (component of PAH).
- Complaints compatible with or established gastroparesis and/or neurogenic bladder
- Any condition that has been recognized as a contra-indication for the use of GLP-1RA and DPP-4i, as listed in the respective SPCs
- History of or actual (severe) mental illness
- Inability to understand the study protocol and/or inability to give informed consent
- History of claustrophobia or presence of metal objects/implants (because of MRI protocol);For the preceding pilot-study:
Similar to the exclusion criteria for the main study, with the additions of:
- Subjects with a fasting plasma glucose *5.6 mmol/L, a 2-hour glucose of *7.8 mmol/L after a 75-grams oral glucose tolerance test, or a HbA1c of *6.5%
- Subjects using any kind of medication

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-05-2013
Enrollment:	70
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Byetta
Generic name:	exenatide
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Inutest
Generic name:	sinistrin
Product type:	Medicine
Brand name:	Januvia
Generic name:	sitagliptin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	para aminohippuric acid ('PAH')
Generic name:	aminohippurate sodium
Product type:	Medicine
Brand name:	Victoza
Generic name:	liraglutide
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	02-11-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-12-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-03-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	15-04-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-02-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-03-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-03-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-05-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-05-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-02-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-03-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
EudraCT	EUCTR2012-003256-36-NL
CCMO	NL41701.029.12
Other	U1111-1130-8248 / NCT01744236