A randomized, placebo, controlled clinical trial to evaluate cardiovascular outcomes after treatment with Exenatide Once Weekly in patients with type 2 diabetes mellitus

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

Summary

ID

NL-OMON41366

Source
ToetsingOnline

Brief title
EXenatide Study of Cardiovascular Event Lowering Trial (EXSCEL)

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
non-insulin dependent diabetes, Type 2 diabetes mellitus

Research involving
Human

Sponsors and support

Primary sponsor: Amylin Pharmaceuticals, LLC
Source(s) of monetary or material Support: Amylin Pharmaceuticals;LLC (a wholly owned subsidiary of Bristol-Myers Squibb)

Intervention

Keyword: Macrovascular events, Phase 3, Type 2 Diabetes mellitus

Outcome measures

Primary outcome

Time to first confirmed CV event in the primary composite CV endpoint

Defined as the time from randomization to first confirmed CV-related death,

nonfatal MI or

nonfatal stroke.

Secondary outcome

Time to all-cause mortality

Defined as time from randomization to death due to any cause.

Time to first confirmed CV event for each component of the primary composite

endpoint

Defined as time from randomization to a confirmed CV-related death, fatal or

nonfatal MI, or

fatal or nonfatal stroke.

Time to hospitalization for acute coronary syndrome

Defined as time from randomization to a confirmed hospital admission for

unstable angina,

ST-elevation myocardial infarction or non-ST-elevation myocardial infarction.

Time to hospitalization for heart failure

Defined as time from randomization to hospital admission for congestive heart

failure

requiring treatment with increased oral or intravenous diuretics, inotropes, or

vasodilator

therapy.

Additional effectivity endpoints can be found in section 8.3 of the protocol.

Study description

Background summary

Type 2 diabetes mellitus is a leading public health issue. Often regarded as a mild disease, it is the fourth leading cause of death in developed countries and the number of people worldwide with diabetes is predicted to exceed 300 million by the year 2025.1 Diabetes remains the leading cause of blindness, end stage renal disease, and lower extremity amputations and confers a two to four times greater risk of heart disease and strokes.

Exenatide, a GLP-1 receptor agonist, has been shown in randomized clinical trials to improve glycemic control, augment endogenous insulin secretion, to reduce blood pressure and promote weight loss with a meta-analysis of exenatide twice-daily (BYETTA) trials showing a trend to
lower relative risk for CV events versus pooled comparators of 0.70 (95% confidence interval 0.38 - 1.31).

Hypotheses:

Efficacy: Bydueron, when used in addition to usual care, is superior to usual care without Bydueron with regard to the risk of developing a confirmed event

in the primary CV composite endpoint.

Safety: Bydueron, when used in addition to usual care, is non-inferior to usual care without Bydueron with regard to the risk of developing a confirmed event in the primary CV composite endpoint.

Study objective

The primary objective of EXSCEL will be to evaluate the effect of Bydueron, used in addition to the current usual care for glycemic control, on major macrovascular events when administered to patients with type 2 diabetes.

Study design

EXSCEL is a multinational pragmatic trial that will be conducted at approximately 800 sites worldwide. It will be run jointly by the Duke Clinical Research Institute (DCRI) and the University of Oxford Diabetes Trials Unit (DTU) Academic Research Organizations (AROs), in an academic collaboration with Amylin Pharmaceuticals, LLC (Amylin), a wholly owned subsidiary of Bristol-Myers Squibb. EXSCEL will be Co-Chaired by Professors Robert Califf (Cardiologist) and Rury Holman (Endocrinologist) and sponsored and funded by Amylin.

Eligible patients will have type 2 diabetes with an HbA1c *6.5% and * 10.0 % on up to three (i.e., 0-3) oral antihyperglycemic agents (AHAs) or insulin either alone or in combination with up to 2 (i.e., 0-2) oral AHAs. Patients enrolled will be at a wide range of CV risk with approximately 70% having had a prior CV event.

The trial will assess the impact of Bydueron therapy upon CV outcomes in a large population from a heterogeneous group of countries and practice environments; patients will be enrolled in the Americas (North/South America), Europe and Asia/Australasia. Given that this population will be at elevated CV risk, it is anticipated that patients will see their usual care provider at least twice per year for routine care. Trial follow up will consist of a blend of trial visits and phone calls during the double-blind placebo-controlled treatment period. There is no requirement to achieve glycemic equipoise between randomized groups but all patients during the double-blind treatment period will have their AHA regimens adjusted as deemed necessary by their usual care provider with the addition or substitution of other AHAs, including insulin, but excluding GLP-1 receptor agonists, to achieve appropriate individualized glycemic goals in line with national guidelines. Adjustments in AHA medications are permitted any time after randomization, but usual care providers will be asked to avoid this until HbA1c levels begin to reflect the initial effect of randomized study medication. Prior to randomization, it is anticipated that all patients will have received counseling regarding appropriate diet and level of

physical activity as part of usual care for type 2 diabetes. Per usual care, HbA1c values should be measured locally. An NGSP(National Glycohemoglobin Standardization Program) certified HbA1c assay should be used if available.

Intervention

A weekly subcutaneous dose of Exenatide 2mg, or placebo administered by the patient.

Study burden and risks

AE's, SAE's, vvital functions and laboratory safety tests are monitored to guard the patient safety and support the evaluation fo the safetyprofile of the drug. The burden for the patient is limited to a minimum by staying in line with the standard care as much as possible, collaborate with the usual care provider and limit study specific procedures.

The risks and burden for the patient are thought to be in perspective with the treatment of the patient and the necessity to study new compounds with extra benefits within the existing standard care.

Contacts

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Amylin Pharmaceuticals, LLC

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Patient has type 2 diabetes mellitus;- Patient will able to see a usual care provider at least twice a year;- Patient has an HbA1c of * 6.5% and * 10.0% and is currently using one of the following treatment regimens: ;*Treatment with up to three (i.e., 0-3) oral AHAs (concomitant use of DPP-4 inhibitors is permitted). ;*Insulin therapy, either alone or in combination with up to two (ie., 0-2) oral AHAs (use of basal and prandial insulins is permitted in any combination of individual or premixed insulins);All patients should be on a stable diabetes management regimen, as assessed by the investigator, at the time of enrollment. ;- Patients with any level of CV risk. ;- Female patients must not be breast feeding and agree to use an effective method of contraception or must not otherwise be at risk of becoming pregnant.;- Patient agrees to provide permission to obtain all medical records necessary for complete data ascertainment during the follow-up period, and agrees to communication between the trial site and the usual care provider in order to facilitate routine care.;- Patient is 18 years or older at enrollment.

Exclusion criteria

- Patient has a diagnosis of type 1 diabetes mellitus, or a history of ketoacidosis.;- Patient has a history (* 2 episodes) of severe hypoglycemia within 12 months of enrollment.;- Patient has ever been treated with an approved or investigational GLP-1 receptor agonist e.g. exenatide BID, exenatide once weekly, liraglutide, lixisenatide, albiglutide, taspoglutide, or dulaglutide.;- Patient is enrolled in another experimental protocol which involves the use of an investigational drug or device, or an intervention that would interfere with the conduct of the trial.;- Patient has a planned or anticipated revascularization procedure.;- Pregnancy or planned pregnancy during the trial period.;- Patient has a history or current evidence of any condition, therapy, laboratory abnormality, or other circumstance which, in the opinion of the investigator or coordinator, might pose an unacceptable risk to the patient, confound the results of the trial e.g. if patient cannot comply with requirements of the trial, or likely to interfere with the patient*s participation for the full duration of the trial.;- Patient has end-stage renal disease or an estimated glomerular filtration rate of <30 mL/min/1.73 m2.;- Patient has a history of gastroparesis.;- Personal or family history of medullary thyroid cancer or MEN2 (Multiple Endocrine Neoplasia Type 2) or calcitonin level > 40ng/L at baseline.;- Patient has previously been enrolled in EXSCEL.;- Patient has a history of pancreatitis.;- Is an employee of Amylin Pharmaceuticals LLC, Bristol-Myers Squibb Company or AstraZeneca.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-08-2014
Enrollment:	204
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Bydueron
Generic name:	Exenatide
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	12-03-2014
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-04-2014
Application type:	First submission

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	28-05-2014
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-06-2014
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-06-2014
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-07-2014
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-08-2014
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-08-2014
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-09-2014
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	05-12-2014
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-12-2014
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-02-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-02-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	18-05-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	EUCTR2010-021069-63-NL
ClinicalTrials.gov	NCT01144338
CCMO	NL47842.028.14