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Complete List of Authors:	Johansen, Nicklas; Steno Diabetes Center Copenhagen, ; Dejgaard, Thomas; Steno Diabetes Center Copenhagen Lund, Asger; Gentofte Hospital, Diabetes Research Division, Internal medicine, Gentofte Hospital Vilsbøll, Tina; Gentofte Hospital, University of Copenhagen, Diabetes Research Division, Department of Internal Medicine Andersen, Henrik; Steno Diabetes Center Copenhagen Knop, Filip K; Gentofte Hospital, University of Copenhagen, Diabetes Research Division, Department of Internal Medicine
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Meal-time administration of exenatide for glycaemic control in type 1 diabetes cases: A randomized, double-blinded, placebo-controlled trial: The MAG1C trial

Nicklas Järvelä Johansen[1], Thomas Fremming Dejgaard[1], Asger Lund[1], Tina Vilsbøll[1,2], Henrik Ullits Andersen[1], Filip Krag Knop[1,2,3]

[1]Steno Diabetes Center Copenhagen, University of Copenhagen, Gentofte, Denmark; [2]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; [3]Novo Nordisk Foundation Center for Basic Metabolic Research; University of Copenhagen, Copenhagen, Denmark

- Correspondence to Filip Krag Knop, Steno Diabetes Center Copenhagen, Kildegårdsvej 28, DK-2900 Hellerup, Denmark; telephone: +45 38674266; e-mail: filipknop@dadlnet.dk

ABSTRACT

Introduction

Persons with type 1 diabetes require intensive insulin therapy to achieve glycaemic control, but side effects, including hypoglycaemia and weight gain, may reduce treatment compliance. We hypothesise that add-on treatment of the short-acting glucagon-like peptide-1 receptor agonist, exenatide, to insulin therapy in persons with type 1 diabetes will reduce insulin requirements, glycaemic excursions and body weight and improve glycaemic control without increasing the risk of hypoglycaemia. The present article describes a protocol developed to test this hypothesis.

Methods and analysis

One hundred adult persons with type 1 diabetes for more than 1 year, insufficient glycaemic control (glycated haemoglobin A1c (HbA1c) between 58 and 86 mmol/mol) and body mass index >22.0 kg/m^2 will be randomized to either exenatide 10 µg three times daily (at meal times) or placebo as add-on therapy to regular basal-bolus insulin treatment for 26 weeks. Primary endpoint is change in HbA1c between the two groups at end of treatment. Secondary endpoints include change in glycaemic excursions (assessed by continuous glucose monitoring); insulin dose; hypoglycaemic- and adverse events; body weight, lean body and fat mass; dietary patterns; quality of life and treatment satisfaction; cardiovascular disease risk profile; metabolomics; and arginine-tested plasma glucose, glucagon and C-peptide levels.

Ethics and dissemination

The study is approved by the Danish Medicines Agency, the Regional Scientific-Ethics Committee of the Capital Region of Denmark and the Data Protection Agency. The study will be carried out under the surveillance and guidance of the Good clinical practice (GCP) unit at Copenhagen University Hospital Bispebjerg in accordance with the ICH-GCP guidelines and the Helsinki Declaration. Positive, negative as well as inconclusive results will be sought disseminated at scientific meetings and in international peer-reviewed scientific journals.

Registration details

ClinicalTrials.gov Identifier: NCT03017352; Eudract-nr.: 2016-001365-92; Regional Scientific-Ethics Committee of the Capital Region of Denmark: H-16034515

STRENGTHS AND LIMITATIONS TO THIS STUDY

- First randomized, double-blinded, placebo-controlled trial to investigate a short-acting glucagon-like peptide-1 receptor agonist as add-on therapy in type 1 diabetes
- This study will include normal- to overweight persons with insufficient glycaemic control, who represent a large proportion of persons with type 1 diabetes world-wide
- The study is powered to draw conclusions on glycaemic control (as assessed by glycated haemoglobin), glycaemic variability and time spent in near-normoglycaemia
- The study may not be sufficiently powered to draw firm conclusions on all secondary endpoints

INTRODUCTION

Background and rationale

Type 1 diabetes is a global disease affecting millions of people with increasing incidence,[1,2]. The majority of persons with type 1 diabetes do not achieve glycaemic control, and up to 50% are overweight or obese with a body mass index >25 kg/m^2,[3–6]. Intensive insulin treatment is necessary to ensure glycaemic control that delays the onset and slows the progression of microvascular complications, i.e. diabetic retinopathy, neuropathy, nephropathy and macrovascular disease,[7–9]. Failure to achieve glycaemic control may occur due to side effects of intensive insulin treatment, i.e. weight gain and hypoglycaemia,[10,11]. Both weight gain and hypoglycaemia have been shown to reduce treatment compliance. Severe hypoglycaemia is associated with serious physiological and psychological comorbidity and even death,[11]. Milder hypoglycaemic episodes lead to fear of future episodes, and unwanted weight gain leads to reduced insulin doses,[12,13]. Overweight itself is unwanted among persons with type 1 diabetes and associated with its own problems, e.g. hypertension, cancer and increased cardiovascular-disease risk,[14].

To improve treatment of type 1 diabetes, these problems must always be considered and addressed. Add-on therapy of non-insulin drugs developed for type 2 diabetes has recently gained increasing interest within type-1-diabetes research,[15]. The incretin hormone, glucagon-like peptide-1 (GLP-1), regulates glucose metabolism through GLP-1 receptor-induced pancreatic and extra-pancreatic effects, e.g. increased glucose-dependent insulin secretion, lowered postprandial glucagon secretion and reduced rate of gastric emptying,[16]. Furthermore, GLP-1 promotes satiety and thereby facilitates body weight loss. Several GLP-1 receptor agonists (GLP-1RAs) are used successfully in the treatment of type 2 diabetes—including insulin-treated persons with type 2 diabetes,[17]. Based on their pharmacokinetic profiles, the GLP-1RAs can be divided into short or long-acting compounds with important between-class differences.

In type 2 diabetes, long-acting compounds exert continuous insulinotropic and glucagonostatic effects. Therefore, they have a greater—and sustained—effect on fasting plasma glucose compared to the short-acting GLP-1RAs. Lowering of fasting plasma glucose is pivotal in insulin-treated type 2 diabetes, and long-acting-compound treatment therefore generally translates into better glycaemic control compared to short-acting GLP-1RAs. In contrast, treatment with short-acting GLP-1RAs exert potent and sustained slowdown of gastric emptying with an effective lowering of postprandial plasma glucose excursions; an effect lost with long-acting GLP-1RAs due to tachyphylaxia,[17]. Thus, persons with adequately controlled fasting plasma glucose that are in need for postprandial glucose-lowering to achieve glycaemic control will most likely benefit more from a short-acting GLP-1RA compared to a long-acting GLP-1RA. In contrast to

the different, glucose-lowering effects of the different GLP-1RAs, the body-weight-reducing effects of GLP-1RAs seem independent of their pharmacokinetic profile,[17].

GLP-1RAs provide a valuable treatment concept for persons with type 2 diabetes. Their insulin-independent effects, i.e. glucose-dependent glucagon suppression (occurring only at plasma glucose concentrations above 4-5 mmol/l), appetite reduction and deceleration of gastric emptying, make them interesting from a type-1-diabetes management perspective. The long-acting GLP-1RA, liraglutide, was previously examined in several randomized, double-blinded, placebo-controlled trials as add-on treatment in persons with type 1 diabetes. These studies indicated substantial reductions in body weight and total exogenous insulin dose and, in general, moderate improvements in glycaemic control, but at the expense of increased incidences of symptomatic hypoglycaemia and hyperglycaemia with ketosis in the two ADJUNCT studies,[19–23].

Importantly, the effect of short-acting compounds on postprandial glucose excursions may be of particular interest as several studies have shown a strong correlation between postprandial glucose control and HbA1c in type 1 diabetes,[18]. However, no large controlled clinical trial evaluating the short-acting GLP-1RA treatment effect in type 1 diabetes has been reported. Smaller, mainly mechanistic, studies of exenatide, a short-acting GLP-1RA normally administered twice daily, have shown reductions in postprandial glucose excursions and insulin requirements (0.17–1.19 U/kg/day) together with weight loss (2.8–4.5 kg) and improved, or at least unaltered, glycaemic control,[24–26]. The main mechanisms for these effects seem to involve deceleration of gastric emptying,[27–29] and possibly reduced postprandial glucagon secretion,[30,31]. Importantly, exenatide given twice daily did not decrease the glucagon response during a hypoglycaemic clamp after 4 weeks of treatment,[32] indicating that exenatide's blood-glucose-lowering effects do not compromise the main counter-regulatory effect during hypoglycaemia.

Hypothesis

We hypothesise that add-on therapy of exenatide 10 ug three times daily at main meals to basal-bolus insulin therapy in normal to overweight/obese persons with type 1 diabetes with inadequate glycaemic control (HbA1c between 58 and 86 mmol/mol) will reduce insulin requirements, glycaemic excursions, body weight and improve glycaemic control without increasing the risk of hypoglycaemia.

Objectives and endpoints

The overall objective of the present study is to evaluate the safety and efficacy of the short-acting GLP-1RA, exenatide, administered three times daily (before each main meal) as add-on therapy to standard basal-bolus insulin regimen in persons with type 1 diabetes. The primary endpoint is change in HbA1c after 26 weeks of treatment compared with placebo. Secondary endpoints include changes in glycaemic excursions;

insulin dose; hypoglycaemic- and adverse events; body weight, lean body mass, fat mass; dietary patterns; quality of life and treatment satisfaction; cardiovascular disease risk profile; metabolomics; and arginine-tested plasma glucose, glucagon and C-peptide levels (Table 1).

Table 1. Primary and secondary endpoints

Primary endpoint
HbA1c
Secondary endpoints
CGM: Glycaemic variability and time spent in hypoglycaemia, near-normoglycaemia and hyperglycaemia
Insulin dose
Hypoglycaemic events
Body weight
BMI
Body composition (hip/waist ratio)
DXA scan: Lean body mass and fat mass composition
Fasting plasma glucose
Dietary patterns
Arginine test: Pre- and post-stimulatory levels of glucagon, C-peptide and glucose
Cardiovascular disease risk profile: Cholesterol levels, biomarkers, blood pressure and heart rate
Quality of life and treatment satisfaction
Adverse events

BMI, body mass index; CGM, continuous glucose monitoring; DXA: dual X-ray absorptiometry; HbA1c, glycated haemoglobin.

Trial design

The MAG1C study (Meal-time Administration of exenatide for Glycaemic control in type 1 diabetes Cases: A randomised, placebo-controlled trial is a 26-week) is an investigator-initiated, two-armed, parallel group, randomized, double-blinded, placebo-controlled study.

METHODS AND ANALYSIS

In total, 100 persons with type 1 diabetes on basal-bolus insulin therapy will be randomized in a 1:1 ratio to either meal-time exenatide 10 µg three times daily or placebo as add-on therapy to regular insulin treatment. A study-independent person will use a computer-generated randomisation list for treatment allocation. Data will be stored in paper-based case report files (CRF). In case of emergency, unblinding will be made on an individual basis not affecting other study participants.

Study population

Study participants will be recruited from outpatient clinics in the Capital Region of Denmark. All recruited participants meeting the eligibility criteria at screening will be enrolled in the study and treated for the following 26 weeks at the Steno Diabetes Center Copenhagen, Gentofte, Denmark (Table 2).

Table 2. Eligibility criteria

Inclusion criteria
Type 1 diabetes according to WHO criteria with duration of ≥1 year
Age ≥18 years
BMI >22.0 kg/m2
HbA1c >7.5% and <10.0% at visit 0 (screening)
Able to count carbohydrates
Able to understand the written patient information and to give informed consent
Exclusion criteria
Insulin pump treatment
Hypoglycaemia unawareness (inability to register low blood glucose)
Diabetic gastroparesis
Compromised kidney function (eGFR <60 ml/min/1.73 m^2, dialysis or kidney transplantation)
Liver disease with elevated plasma alanine aminotransferase > three times the upper limit of normal (measured at visit 0 with the possibility of one repeat analysis within a week, and the last measured value as being conclusive)
History of acute and/or chronic pancreatitis
Subjects with personal or family history of medullary carcinoma or MEN syndrome
Inflammatory bowel disease
Cancer, unless in complete remission for >5 years
Proliferative retinopathy
Other concomitant disease or treatment that according to the investigator's assessment makes the patient unsuitable for study participation
Alcohol/drug abuse
Fertile women not using chemical (tablet/pill, depot injection of progesterone, subdermal gestagen implantation, hormonal vaginal ring or transdermal hormonal patch) or mechanical (spirals) contraceptives
Pregnant or nursing women
Known or suspected hypersensitivity to trial product or related products
Receipt of an investigational drug within 30 days prior to visit 0
Simultaneous participation in any other clinical intervention trial
Withdrawal criteria
In case of pregnancy (or desire for pregnancy), female subjects are withdrawn
Lack of compliance to any of the important study procedures in the discretion of the investigator
Onset of any disorder considered to compromise the safety by participating in the study
Unacceptable adverse effects in the discretion of the investigator
Withdrawal on participants request will be accepted at any time without further justification

BMI, body mass index; eGFR, estimated glomerular filtration Rate; HbA1c, glycated haemoglobin; MEN, multiple endocrine neoplasia types 1 and 2; WHO, World Health Organization.

Trial visits and examinations

Written and oral study information will be provided to study participants by the investigator before obtaining written informed consent. At screening (visit 0), information on demography, medical history, smoking/drinking status and concomitant medication will be obtained. Further, a physical assessment will be made including heart rate, blood pressure, body weight, hip/waist ratio and electrocardiography together with blood samples and urine tests (Table 3). Six-day continuous glucose monitoring (CGM), together with a 3-day diet recording, will be made before randomization (visit 1), at week 4 (visit 2) and at end of treatment (visit 4). Participants not familiar with carbohydrate counting will be offered a standard course before entering the study. Blood samples and urine tests will be taken during the trial (Table 3). An arginine test and a dual-energy X-ray (DXA) absorption scan will be made at randomization (visit 1) and at end of treatment (visit 4) (Table 3). Insulin doses will be adjusted during the trial based on seven-point plasma glucose profiles, CGM and HbA1c. Blood-glucose treatment targets will be based on international guidelines,[9], *i.e.* preprandial values of 4–7 mmol/l and postprandial values <10 mmol/l. Following randomization, no changes in insulin types are allowed. The study participants will be asked to fill out questionnaires on quality of life (ADDQoL) and Diabetes treatment satisfactory questionnaire: status (DTSQs) and change version (DTSQc),[33,34]. Information on adverse events; current medication; basal-bolus insulin dose; hypoglycaemic events; and consultation blood pressure and heart rate will be recorded at all visits. Body weight and waist/hip ratio will be measured as well, except on visit 3. Between-visit telephone contacts will be made to ensure the study participants' safety and compliance together with evaluation of insulin treatment. Further, the study participants will be instructed to contact the study team if any insulin-dosing or glucose control problems occur. All contacts will be recorded in the CRF (Figure 1 and Table 4).

Table 3. Blood samples

Screening and control visits
Blood haemoglobin, leucocytes, thrombocytes, plasma glucose, potassium, sodium, creatinine, TSH, cholesterol, triglycerides, ALT, AST, amylase, lipase, serum albumin, total serum-ketones, beta-hydroxybutyrate and acetoacetate
Biobank
CVD markers: HsCRP, pro-BNP
Bone markers: CTX, P1NP, sclerostin, osteocalcin
Inflammation markers: IL-2, IL-6, TNF-α
Urine albumin-creatinine ratio, hCG
Arginine test
Glucagon, C-peptide, plasma glucose

ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; C-peptide, Connecting peptide; CTX, C-terminal telopeptide of type 1; CVD, Cardiovascular disease; hCG, Human choriongonadotropin; hsCRP, High-sensitivity C reactive protein; IL-2, Interleukin-2; IL-6, Interleukin-6, P1NP, Serum type 1 procollagen N-terminal; pro-BNP, Prohormone brain natriuretic peptide; TNF-α, Tumour necrosis factor-alpha; TSH, Thyroid-stimulating hormone

Table 4. Trial outline

Visit	Visit 0 Screening	Visit 1 Randomization	Telephone contact	Telephone contact	Visit 2 Clinical control	Telephone contact	Visit 3 Clinical control	Telephone contact	Telephone contact	Visit 4 End of treatment	Safety follow-up
Time (weeks)	- 4 ± 2	0	1	2	4 ± 2	8 ± ½	12 ± ½	16 ± ½	20 ± ½	26 ± 1	26 + 2
General											
Informed consent	X										
Assessment of in- and exclusion criteria	X										
Demography	X										
Medical history	X										
Smoking, alcohol	X										
Concomitant medication	X	X	X	X	X	X	X	X	X	X	
Endpoints											
HbA1c	X	X					X			X	
Weight, BMI, waist/hip ratio	X	X					X			X	
Insulin dose	X	X	X	X	X	X	X	X	X	X	
Hypoglycaemic events	X	X	X	X	X	X	X	X	X	X	
CGM for 6 days, incl. registration of carb counting	X				X					X	
7-point PG profile (prior)		X			X		X			X	
DXA scan		X								X	
ADDQoL		X					X			X	
DTSQs		X					X			X	
DTSQc										X	
Diet recording	X				X					X	
Clinical assessment											
Physical assessment including height	X										
Consultation blood pressure and heart rate	X	X			X		X			X	
ECG	X										
Arginine test		X								X	
Safety											
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Blood tests	X	X			X		X			X	
Ketones	X	X			X		X			X	
Biobank		X			X		X			X	
Urinary albumin:creatinine ratio		X					X			X	
Urinary HCG	X	(X)			(X)		(X)			(X)	
Study medication											
Dispensing visits		X			X		X				
Drug accountability					X		X			X	
Study drug dose titration				X							

7-point PG profile, 7-point plasma glucose profile; ADDQoL, The Audit of Diabetes-Dependent Quality of Life; Blood tests, blood haemoglobin, leucocytes and thrombocytes, plasma glucose, potassium, sodium, creatinine, lipids, alanine aminotransferase, aspartate aminotransferase, amylase

and lipase, and serum albumin, total serum-ketones, beta-hydroxybutyrate, acetoacetate and cardiovascular disease markers; BMI, Body mass index; CGM, Continous glucose monitoring; DTSQs, Diabetes treatment satisfactory questionnaire – status version; DTSQc, Diabetes treatment satisfactory questionnaire – change version; DXA scan, Dual x-ray absorptiometry scan; ; ECG, Electrocardiography; HbA1c, glycated haemoglobin; Ketones, measured with FreeStyle Precision β-Ketone© in the finger; Urinary albumin:creatinine ratio, three-day urine collection (morning spot test); Urinary HCG, urinary human choriongonadotropin pregnancy test will be performed if menstruation is absent in a woman of childbearing potential

Intervention

Name: Byetta™ (exenatide) or matching placebo.

Pharmaceutical form: Exenatide 0.25 mg/ml, 3 ml cartridges in a reusable Ypsopen™, for subcutaneous injection. Placebo, 3 ml cartridges in a reusable Ypsopen™, for subcutaneous injection.

Pharmaceutical dosage: To minimize the side-effect risk, exenatide dose, or placebo, will be increased from initial 5 µg three times daily to full dosage, 10 µg three times daily, two weeks after randomization. The injection must occur within one hour before the main meals. Dose increments can be titrated based on the individual study participant's study-drug tolerance, to a minimum of 5 µg three times daily three months after randomization. If not possible at this time, the participant will be withdrawn from the study.

Side effects: Common side effects (1-10%) include nausea, vomiting, diarrhoea, hypoglycaemia and headache. Study participants will be carefully instructed to avoid dehydration if gastrointestinal side effects occur.

Shipping and packing: All study medication will be produced, blinded, packed and delivered by AstraZeneca, the producer of Byetta™.

Sample size

To be able to detect a difference in change in HbA1c (primary outcome) between study arms of 6 mmol/mol with 80% power, a 5% significance level and a presumed 9 mmol/mol standard deviation, 42 persons should be included in each study arm (two-sided test). To allow for a 20% dropout rate, 100 persons in total will be included in the study: 50 in each study arm. The sample size calculation is based on data from a similar study on the GLP-1RA, liraglutide,[21]. Withdrawn study participants will not be replaced.

Data analysis

The per-protocol study population includes all participants who complete the study with a documented, valid baseline and end-of-treatment assessment of the primary endpoint without any major protocol violations. In case of drop-out, last observation is carried forward. The intention-to-treat population includes all randomized persons. Primary-endpoint analysis will be based on the per-protocol population. Absolute differences and adjusted mean changes between groups, together with 95% confidence intervals, will be reported. The efficacy analysis will be carried out with a linear mixed-effect model with visit, treatment and their interaction as fixed factors and a random intercept on the person level. Variables that are normally distributed will be presented as mean ± standard deviation or standard error of the mean. In

case of non-normal distribution, non-parametric statistics and log transformation will be used. A two-tailed p value ≤0.05 will be considered statistically significant. Additional analyses will be made from the intention-to-treat population to assess the validity of the per-protocol-population conclusions if loss of follow-up occurs. These calculations will include duration in study and reason for discontinuation.

ETHICS AND DISSEMINATION

We expect the present study to generate important information about the use of short-acting GLP-1RAs as add-on therapy to insulin in persons with type 1 diabetes. We expect to be able to answer two questions relevant for numerous persons world-wide: Will meal-time exenatide 10 µg added three times daily (at each main meal) to regular insulin therapy 1) improve postprandial glycaemic excursions and 2) provide improved, long-term glycaemic control measured as HbA1c and glycaemic variability?

During the study, a physician will follow each participant with careful evaluation of insulin treatment with glycaemic optimization and study-drug safety and efficacy. This is expected to lower the adverse-event risk. Exenatide is approved for the treatment of type 2 diabetes by the European Medicines Agency and by the US Food and Drug Administration. Prior studies have shown limited side effects such as nausea, vomiting, hypoglycaemia and headache. Nausea and vomiting, generally transient, usually occur within three weeks after treatment initiation. They can be minimized by gradual dose titration, as planned in this study. The hypoglycaemia risk is reduced by insulin-dose reduction at study start and by instructing participants in careful blood glucose monitoring. Few cases of acute pancreatitis have been reported in persons with type 2 diabetes using exenatide, but the incidence was similar to the type-2-diabetes background population. Overall, the risk of side effects in this study is expected to be modest. Arginine injection is a well-validated, safe method to evaluate pancreatic alpha and beta cell function, but potentially associated with transient mild flushing, nausea and metallic taste. Vein puncture may cause a short pain, risk of a small haematoma and a minimal risk of puncture-site infection. In total, 400 ml blood and 80 ml of urine per person will be collected throughout the study. At the two DXA scans, participants will be exposed to weak X-ray radiation (less than 1 mSv in total). For comparison, the background radiation in Denmark is about 3 mSv per year. The risk of complications, or adverse events, is negligible for all other planned study procedures.

Data will be processed and merged into one or more scientific articles and published in accordance with the CONSORT 2010 statement in international, peer-reviewed scientific journals and presented at national and international scientific meetings. Positive, negative and inconclusive results will be published as soon as scientifically justifiable. AstraZeneca commented on the study design but will have no influence on trial conduction, data analysis, interpretation or publication.

Study approval

The MAG1C trial is approved by the Danish Medicines Authority (Eudract-nr.: 2016-001365-92), the Regional Scientific-Ethics Committee of the Capital Region of Denmark (H-16034515) and the Data Protection Agency (2012-58-0004). It is registered at ClinicalTrials.gov (NCT03017352). The study will be conducted under the surveillance and guidance of the Good clinical practice (GCP) unit at Copenhagen University Hospital Bispebjerg in accordance with the ICH-GCP guidelines and the Helsinki Declaration. The study commenced in January 2017 and is expected to be reported in 2019.

AUTHOR'S CONTRIBUTIONS

NJJ, TFD, AL, TV, HUA and FKK conceived and designed the study. FKK is guarantor of the study and sponsors the trial. NJJ drafted the manuscript and all authors have contributed to the revision of the manuscript and read and approved the final version of the manuscript.

COMPETING INTERESTS STATEMENT

NJJ and TV have no competing interests. TFD has received research support from Novo Nordisk and AstraZeneca, and has received lecture fees from Novo Nordisk. AL has received lecture fees from Novo Nordisk, Boehringer Ingelheim and Eli Lilly. HUA owns stocks in Novo Nordisk and serves in advisory boards for Novo Nordisk and Astra Zeneca. FKK has served on scientific advisory panels and/or speaker's bureaus for, served as a consultant to and/or received research support from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Gubra, MSD/Merck, Novo Nordisk, Sanofi and Zealand Pharma.

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Figure 1. Flowchart

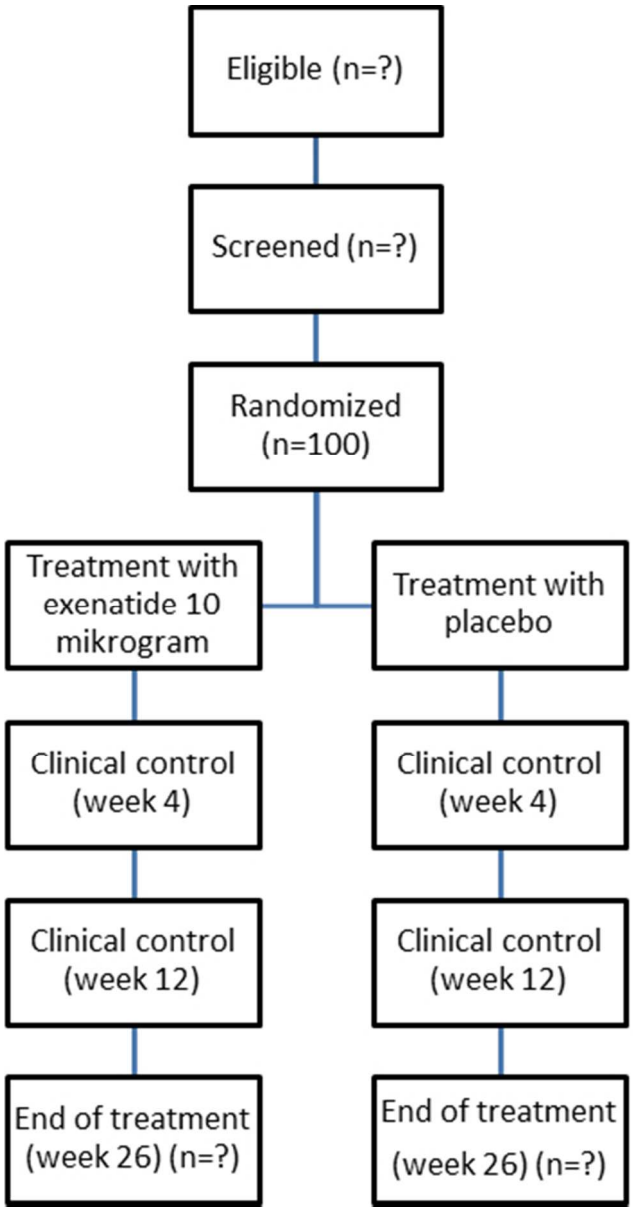

Figure 1. Flowchart

73x140mm (120 x 120 DPI)

BMJ Open

Protocol for Meal-time administration of exenatide for glycaemic control in type 1 diabetes cases (The MAG1C trial): a randomized, double-blinded, placebo-controlled trial

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Protocol for Meal-time administration of exenatide for glycaemic control in type 1 diabetes cases (The MAG1C trial): a randomized, double-blinded, placebo-controlled trial

Nicklas Järvelä Johansen[1], Thomas Fremming Dejgaard[1], Asger Lund[1], Tina Vilsbøll[1,2], Henrik Ullits Andersen[1], Filip Krag Knop[1,2,3]

[1]Steno Diabetes Center Copenhagen, University of Copenhagen, Gentofte, Denmark; [2]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; [3]Novo Nordisk Foundation Center for Basic Metabolic Research; University of Copenhagen, Copenhagen, Denmark

Correspondence to Filip Krag Knop, Steno Diabetes Center Copenhagen, Kildegårdsvej 28, DK-2900 Hellerup, Denmark; telephone: +45 38674266; e-mail: filipknop@dadlnet.dk

ABSTRACT

Introduction

Persons with type 1 diabetes require intensive insulin therapy to achieve glycaemic control, but side effects, including hypoglycaemia and weight gain, may reduce treatment compliance. We hypothesise that add-on treatment of the short-acting glucagon-like peptide-1 receptor agonist, exenatide, to insulin therapy in persons with type 1 diabetes will reduce insulin requirements, glycaemic excursions and body weight and improve glycaemic control without increasing the risk of hypoglycaemia. The present article describes a protocol developed to test this hypothesis.

Methods and analysis

One hundred adult persons with type 1 diabetes for more than 1 year, insufficient glycaemic control (glycated haemoglobin A1c (HbA1c) between 58 and 86 mmol/mol) and body mass index >22.0 kg/m^2 will be randomized to either exenatide 10 µg three times daily (at meal times) or placebo as add-on therapy to regular basal-bolus insulin treatment for 26 weeks. Primary endpoint is change in HbA1c between the two groups at end of treatment. Secondary endpoints include change in glycaemic excursions (assessed by continuous glucose monitoring); insulin dose; hypoglycaemic- and adverse events; body weight, lean body and fat mass; dietary patterns; quality of life and treatment satisfaction; cardiovascular disease risk profile; metabolomics; and arginine-tested plasma glucose, glucagon and C-peptide levels.

Ethics and dissemination

The study is approved by the Danish Medicines Agency, the Regional Scientific-Ethics Committee of the Capital Region of Denmark and the Data Protection Agency. The study will be carried out under the surveillance and guidance of the Good clinical practice (GCP) unit at Copenhagen University Hospital Bispebjerg in accordance with the ICH-GCP guidelines and the Helsinki Declaration. Positive, negative as well as inconclusive results will be sought disseminated at scientific meetings and in international peer-reviewed scientific journals.

Registration details

ClinicalTrials.gov Identifier: NCT03017352; Eudract-nr.: 2016-001365-92; Regional Scientific-Ethics Committee of the Capital Region of Denmark: H-16034515

STRENGTHS AND LIMITATIONS TO THIS STUDY

- First randomized, double-blinded, placebo-controlled trial to investigate a short-acting glucagon-like peptide-1 receptor agonist as add-on therapy in type 1 diabetes
- This study will include normal- to overweight persons with insufficient glycaemic control, who represent a large proportion of persons with type 1 diabetes world-wide
- The study is powered to draw conclusions on glycaemic control (as assessed by glycated haemoglobin), glycaemic variability and time spent in near-normoglycaemia
- The study may not be sufficiently powered to draw firm conclusions on all secondary endpoints

INTRODUCTION

Background and rationale

Type 1 diabetes is a global disease affecting millions of people with increasing incidence,[1,2]. The majority of persons with type 1 diabetes do not achieve glycaemic control, and up to 50% are overweight or obese with a body mass index >25 kg/m^2,[3–6]. Intensive insulin treatment is necessary to ensure glycaemic control that delays the onset and slows the progression of microvascular complications, i.e. diabetic retinopathy, neuropathy, nephropathy and macrovascular disease,[7–9]. Failure to achieve glycaemic control may occur due to side effects of intensive insulin treatment, i.e. weight gain and hypoglycaemia,[10,11]. Both weight gain and hypoglycaemia have been shown to reduce treatment compliance. Severe hypoglycaemia is associated with serious physiological and psychological comorbidity and even death,[11]. Milder hypoglycaemic episodes lead to fear of future episodes, and unwanted weight gain leads to reduced insulin doses,[12,13]. Overweight itself is unwanted among persons with type 1 diabetes and associated with its own problems, e.g. hypertension, cancer and increased cardiovascular-disease risk,[14].

To improve treatment of type 1 diabetes, these problems must always be considered and addressed. Add-on therapy of non-insulin drugs developed for type 2 diabetes has recently gained increasing interest within type-1-diabetes research,[15]. The incretin hormone, glucagon-like peptide-1 (GLP-1), regulates glucose metabolism through GLP-1 receptor-induced pancreatic and extra-pancreatic effects, e.g. increased glucose-dependent insulin secretion, lowered postprandial glucagon secretion and reduced rate of gastric emptying,[16]. Furthermore, GLP-1 promotes satiety and thereby facilitates body weight loss. Several GLP-1 receptor agonists (GLP-1RAs) are used successfully in the treatment of type 2 diabetes—including insulin-treated persons with type 2 diabetes,[17]. Based on their pharmacokinetic profiles, the GLP-1RAs can be divided into short or long-acting compounds with important between-class differences.

In type 2 diabetes, long-acting compounds exert continuous insulinotropic and glucagonostatic effects. Therefore, they have a greater—and sustained—effect on fasting plasma glucose compared to the short-acting GLP-1RAs. Lowering of fasting plasma glucose is pivotal in insulin-treated type 2 diabetes, and long-acting-compound treatment therefore generally translates into better glycaemic control compared to short-acting GLP-1RAs. In contrast, treatment with short-acting GLP-1RAs exert potent and sustained slowdown of gastric emptying with an effective lowering of postprandial plasma glucose excursions; an effect lost with long-acting GLP-1RAs due to tachyphylaxia,[17]. Thus, persons with adequately controlled fasting plasma glucose that are in need for postprandial glucose-lowering to achieve glycaemic control will most likely benefit more from a short-acting GLP-1RA compared to a long-acting GLP-1RA [18]. In contrast

to the different, glucose-lowering effects of the different GLP-1RAs, the body-weight-reducing effects of GLP-1RAs seem independent of their pharmacokinetic profile,[17].

GLP-1RAs provide a valuable treatment concept for persons with type 2 diabetes. Their insulin-independent effects, i.e. glucose-dependent glucagon suppression (occurring only at plasma glucose concentrations above 4-5 mmol/l), appetite reduction and deceleration of gastric emptying, make them interesting from a type-1-diabetes management perspective. The long-acting GLP-1RA, liraglutide, was previously examined in several randomized, double-blinded, placebo-controlled trials as add-on treatment in persons with type 1 diabetes. These studies indicated substantial reductions in body weight and total exogenous insulin dose and, in general, moderate improvements in glycaemic control, but at the expense of increased incidences of symptomatic hypoglycaemia and hyperglycaemia with ketosis in the two ADJUNCT studies,[19–23].

Importantly, the effect of short-acting compounds on postprandial glucose excursions may be of particular interest as several studies have shown a strong correlation between postprandial glucose control and HbA1c in type 1 diabetes,[18]. However, no large controlled clinical trial evaluating the short-acting GLP-1RA treatment effect in type 1 diabetes has been reported. Smaller, mainly mechanistic, studies of exenatide, a short-acting GLP-1RA normally administered twice daily, have shown reductions in postprandial glucose excursions and insulin requirements (0.17–1.19 U/kg/day) together with weight loss (2.8–4.5 kg) and improved, or at least unaltered, glycaemic control,[24–26]. The main mechanisms for these effects seem to involve deceleration of gastric emptying,[27–29] and possibly reduced postprandial glucagon secretion,[30,31]. Importantly, exenatide given twice daily did not decrease the glucagon response during a hypoglycaemic clamp after 4 weeks of treatment,[32] indicating that exenatide's blood-glucose-lowering effects do not compromise the main counter-regulatory effect during hypoglycaemia.

Hypothesis

We hypothesise that add-on therapy of exenatide 10 ug three times daily at main meals to basal-bolus insulin therapy in normal to overweight/obese persons with type 1 diabetes with inadequate glycaemic control (HbA1c between 58 and 86 mmol/mol) will reduce insulin requirements, glycaemic excursions, body weight and improve glycaemic control without increasing the risk of hypoglycaemia.

Objectives and endpoints

The overall objective of the present study is to evaluate the safety and efficacy of the short-acting GLP-1RA, exenatide, administered three times daily (before each main meal) as add-on therapy to standard basal-bolus insulin regimen in persons with type 1 diabetes. The primary endpoint is change in HbA1c after 26 weeks of treatment compared with placebo. Secondary endpoints include changes in glycaemic excursions;

insulin dose; hypoglycaemic- and adverse events; body weight, lean body mass, fat mass; dietary patterns; quality of life and treatment satisfaction; cardiovascular disease risk profile; metabolomics; and arginine-tested plasma glucose, glucagon and C-peptide levels (Table 1).

Table 1. Primary and secondary endpoints

Primary endpoint
HbA1c
Secondary endpoints
CGM: Glycaemic variability and time spent in hypoglycaemia, near-normoglycaemia and hyperglycaemia
Insulin dose
Hypoglycaemic events
Body weight
BMI
Body composition (hip/waist ratio)
DXA scan: Lean body mass and fat mass composition
Fasting plasma glucose
Dietary patterns
Arginine test: Pre- and post-stimulatory levels of glucagon, C-peptide and glucose
Cardiovascular disease risk profile: Cholesterol levels, biomarkers, blood pressure and heart rate
Quality of life and treatment satisfaction
Adverse events

BMI, body mass index; CGM, continuous glucose monitoring; DXA: dual X-ray absorptiometry; HbA1c, glycated haemoglobin.

Trial design

The MAG1C study (Meal-time Administration of exenatide for Glycaemic control in type 1 diabetes Cases: A randomised, placebo-controlled trial is a 26-week) is an investigator-initiated, two-armed, parallel group, randomized, double-blinded, placebo-controlled study.

METHODS AND ANALYSIS

In total, 100 persons with type 1 diabetes on basal-bolus insulin therapy will be randomized in a 1:1 ratio to either meal-time exenatide 10 µg three times daily or placebo as add-on therapy to regular insulin treatment. A study-independent person will use a computer-generated randomisation list for treatment allocation. Data will be stored in paper-based case report files (CRF). Double data entry into a digital database with range checks for data values will be used. In case of emergency, unblinding will be made on an individual basis not affecting other study participants. All data will be pseudo-anonymised.

Study population

Study participants will be recruited from outpatient clinics in the Capital Region of Denmark. All recruited participants meeting the eligibility criteria at screening will be enrolled in the study and treated for the following 26 weeks at the Steno Diabetes Center Copenhagen, Gentofte, Denmark (Table 2).

Table 2. Eligibility criteria

Inclusion criteria
Type 1 diabetes according to WHO criteria with duration of ≥1 year
Age ≥18 years
BMI >22.0 kg/m2
HbA1c >7.5% and <10.0% at visit 0 (screening)
Able to count carbohydrates
Able to understand the written patient information and to give informed consent
Exclusion criteria
Insulin pump treatment
Hypoglycaemia unawareness (inability to register low blood glucose)
Diabetic gastroparesis
Compromised kidney function (eGFR <60 ml/min/1.73 m^2, dialysis or kidney transplantation)
Liver disease with elevated plasma alanine aminotransferase > three times the upper limit of normal (measured at visit 0 with the possibility of one repeat analysis within a week, and the last measured value as being conclusive)
History of acute and/or chronic pancreatitis
Subjects with personal or family history of medullary carcinoma or MEN syndrome
Inflammatory bowel disease
Cancer, unless in complete remission for >5 years
Proliferative retinopathy
Other concomitant disease or treatment that according to the investigator's assessment makes the patient unsuitable for study participation
Alcohol/drug abuse
Fertile women not using chemical (tablet/pill, depot injection of progesterone, subdermal gestagen implantation, hormonal vaginal ring or transdermal hormonal patch) or mechanical (spirals) contraceptives
Pregnant or nursing women
Known or suspected hypersensitivity to trial product or related products
Receipt of an investigational drug within 30 days prior to visit 0
Simultaneous participation in any other clinical intervention trial
Withdrawal criteria
In case of pregnancy (or desire for pregnancy), female subjects are withdrawn
Lack of compliance to any of the important study procedures in the discretion of the investigator
Onset of any disorder considered to compromise the safety by participating in the study
Unacceptable adverse effects in the discretion of the investigator
Withdrawal on participants request will be accepted at any time without further justification

BMI, body mass index; eGFR, estimated glomerular filtration Rate; HbA1c, glycated haemoglobin; MEN, multiple endocrine neoplasia types 1 and 2; WHO, World Health Organization.

Trial visits and examinations

Study participants will be provided with written and oral information by the investigator prior to obtaining written informed consent at Steno Diabetes Center Copenhagen. At screening (visit 0), information on demography, medical history, smoking/drinking status and concomitant medication will be obtained. Further, a physical assessment will be made including heart rate, blood pressure, body weight, hip/waist ratio and electrocardiography together with blood samples and urine tests (Table 3). Six-day continuous glucose monitoring (CGM), together with a 3-day diet recording, will be made before randomization (visit 1), at week 4 (visit 2) and at end of treatment (visit 4). Participants not familiar with carbohydrate counting will be offered a standard course before entering the study. Blood samples and urine tests will be taken during the trial (Table 3). An arginine test and a dual-energy X-ray (DXA) absorption scan will be made at randomization (visit 1) and at end of treatment (visit 4) (Table 3). Insulin doses will be adjusted by the investigator or qualified study personnel during the trial at study visits based on seven-point plasma glucose profiles, CGM and HbA1c. Blood-glucose treatment targets will be based on international guidelines [9], i.e. preprandial values of 4–7 mmol/l and postprandial values <10 mmol/l. Following randomisation, changes in insulin types are not allowed. The study participants will be asked to fill out questionnaires on quality of life (ADDQoL) and Diabetes treatment satisfactory questionnaire: status (DTSQs) and change version (DTSQc),[33,34]. Information on adverse events; current medication; basal-bolus insulin dose; hypoglycaemic events; and consultation blood pressure and heart rate will be recorded at all visits. Body weight and waist/hip ratio will be measured as well, except on visit 3. Between-visit telephone contacts will be made to ensure the study participants' safety and compliance together with evaluation of insulin treatment. Further, the study participants will be instructed to contact the study team if any insulin-dosing or glucose control problems occur. All contacts will be recorded in the CRF (Figure 1 and Table 4). To further attenuate the risk of hypoglycaemia, no insulin is taken on the visit 1 study day and plasma glucose is measured before administration of the first dose of investigational product and 30 minutes following ingestion of a standardised meal. Next, telephone contacts are made one and two weeks after randomisation with careful instruction on reporting any hypoglycaemic and hyperglycaemic events. Finally, the investigational product is started at 5 microgram and escalated to 10 microgram following telephone contact 2, if tolerated. All contacts will be recorded in the CRF (Figure 1 and Table 4). Finally to ensure compliance, used investigational product cartridges will be collected at study visit.

A sub-study on the role of the microbial gut flora, approved by the Danish regulatory authorities and voluntary to participate in, involving the collection of faecal specimens at each study visit will also be conducted.

Patient and public involvement

The MAG1C study aims to attenuate intensive insulin treatments' side effects: hypoglycaemia and weight gain. Further, our study drug regimen will, hopefully, make it easier to control blood glucose excursions on a daily basis. We evaluate study-participant treatment satisfaction and quality of life through questionnaires during the study period to make sure our results benefit persons with type 1 diabetes. Study participants will be informed of our results in layman-terms as well as their individual exenatide/placebo assignment by letters following publication. Finally during the study protocol write-up, a colleague of ours with type 1 diabetes read and commented on the final protocol draft.

Table 3. Blood samples

Screening and control visits
Blood haemoglobin, leucocytes, thrombocytes, plasma glucose, potassium, sodium, creatinine, TSH, cholesterol, triglycerides, ALT, AST, amylase, lipase, serum albumin, total serum-ketones, beta-hydroxybutyrate and acetoacetate
Biobank
CVD markers: HsCRP, pro-BNP
Bone markers: CTX, P1NP, sclerostin, osteocalcin
Inflammation markers: IL-2, IL-6, TNF-α
Urine albumin-creatinine ratio, hCG
Arginine test
Glucagon, C-peptide, plasma glucose

ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; C-peptide, Connecting peptide; CTX, C-terminal telopeptide of type 1; CVD, Cardiovascular disease; hCG, Human choriongonadotropin; hsCRP, High-sensitivity C reactive protein; IL-2, Interleukin-2; IL-6, Interleukin-6, P1NP, Serum type 1 procollagen N-terminal; pro-BNP, Prohormone brain natriuretic peptide; TNF-α, Tumour necrosis factor-alpha; TSH, Thyroid-stimulating hormone

Table 4. Trial outline

Visit	Visit 0 Screening	Visit 1 Randomization	Telephone contact	Telephone contact	Visit 2 Clinical control	Telephone contact	Visit 3 Clinical control	Telephone contact	Telephone contact	Visit 4 End of treatment	Safety follow-up
Time (weeks)	- 4 ± 2	0	1	2	4 ± 2	8 ± ½	12 ± ½	16 ± ½	20 ± ½	26 ± 1	26 + 2
General											
Informed consent	X										
Assessment of in- and exclusion criteria	X										
Demography	X										
Medical history	X										
Smoking, alcohol	X										
Concomitant medication	X	X	X	X	X	X	X	X	X	X	
Endpoints											
HbA1c	X	X					X			X	
Weight, BMI, waist/hip ratio	X	X					X			X	
Insulin dose	X	X	X	X	X	X	X	X	X	X	
Hypoglycaemic events	X	X	X	X	X	X	X	X	X	X	
CGM for 6 days, incl. registration of carb counting	X				X					X	
7-point PG profile (prior)		X			X		X			X	
DXA scan		X								X	
ADDQoL		X					X			X	
DTSQs		X					X			X	
DTSQc										X	
Diet recording	X				X					X	
Clinical assessment											
Physical assessment including height	X										
Consultation blood pressure and heart rate	X	X			X		X			X	
ECG	X										
Arginine test		X								X	
Safety											
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Blood tests	X	X			X		X			X	
Ketones	X	X			X		X			X	
Biobank		X			X		X			X	
Urinary albumin:creatinine ratio		X					X			X	
Urinary HCG	X	(X)			(X)		(X)			(X)	
Study medication											
Dispensing visits		X			X		X				
Drug accountability					X		X			X	
Study drug dose titration				X							

7-point PG profile, 7-point plasma glucose profile; ADDQoL, The Audit of Diabetes-Dependent Quality of Life; Blood tests, blood haemoglobin, leucocytes and thrombocytes, plasma glucose, potassium, sodium, creatinine, lipids, alanine aminotransferase, aspartate aminotransferase, amylase

and lipase, and serum albumin, total serum-ketones, beta-hydroxybutyrate, acetoacetate and cardiovascular disease markers; BMI, Body mass index; CGM, Continous glucose monitoring; DTSQs, Diabetes treatment satisfactory questionnaire – status version; DTSQc, Diabetes treatment satisfactory questionnaire – change version; DXA scan, Dual x-ray absorptiometry scan; ; ECG, Electrocardiography; HbA1c, glycated haemoglobin; Ketones, measured with FreeStyle Precision β-Ketone© in the finger; Urinary albumin:creatinine ratio, three-day urine collection (morning spot test); Urinary HCG, urinary human choriongonadotropin pregnancy test will be performed if menstruation is absent in a woman of childbearing potential

Intervention

Name: Byetta™ (exenatide) or matching placebo.

Pharmaceutical form: Exenatide 0.25 mg/ml, 3 ml cartridges in a reusable Ypsopen™, for subcutaneous injection. Placebo, 3 ml cartridges in a reusable Ypsopen™, for subcutaneous injection.

Pharmaceutical dosage: To minimize the side-effect risk, exenatide dose, or placebo, will be increased from initial 5 µg three times daily to full dosage, 10 µg three times daily, two weeks after randomization. The injection must occur within one hour before the main meals. Dose increments can be titrated based on the individual study participant's study-drug tolerance, to a minimum of 5 µg three times daily three months after randomization. If not possible at this time, the participant will be withdrawn from the study.

Side effects: Common side effects (1-10%) include nausea, vomiting, diarrhoea, hypoglycaemia and headache. Study participants will be carefully instructed to avoid dehydration if gastrointestinal side effects occur.

Shipping and packing: All study medication will be produced, blinded, packed and delivered by AstraZeneca, the producer of Byetta™.

Sample size

To be able to detect a difference in change in HbA1c (primary outcome) between study arms of 6 mmol/mol with 80% power, a 5% significance level and a presumed 9 mmol/mol standard deviation, 42 persons should be included in each study arm (two-sided test). To allow for a 20% dropout rate, 100 persons in total will be included in the study: 50 in each study arm. The sample size calculation is based on data from a similar study on the GLP-1RA, liraglutide,[21]. Withdrawn study participants will not be replaced.

Data analysis

The per-protocol study population includes all participants who complete the study with a documented, valid baseline and end-of-treatment assessment of the primary endpoint without any major protocol violations. In case of drop-out, last observation is carried forward. The intention-to-treat population includes all randomized persons. Primary-endpoint analysis will be based on the per-protocol population. Absolute differences and adjusted mean changes between groups, together with 95% confidence intervals, will be reported. The efficacy analysis will be carried out with a linear mixed-effect model with visit, treatment and their interaction as fixed factors and a random intercept on the person level. Variables that are normally distributed will be presented as mean ± standard deviation or standard error of the mean. In

case of non-normal distribution, non-parametric statistics and log transformation will be used. A two-tailed p value ≤0.05 will be considered statistically significant. Additional analyses will be made from the intention-to-treat population to assess the validity of the per-protocol-population conclusions if loss of follow-up occurs. These calculations will include duration in study and reason for discontinuation.

Following completion of last patient last visit, unblinding will be made in two steps. During data analysis, unblinding will be made on group level, i.e. participants are assigned to group 1 and 2. After the pre-specified data analysis is completed, the specific treatment group will be revealed.

ETHICS AND DISSEMINATION

We expect the present study to generate important information about the use of short-acting GLP-1RAs as add-on therapy to insulin in persons with type 1 diabetes. We expect to be able to answer two questions relevant for numerous persons world-wide: Will meal-time exenatide 10 µg added three times daily (at each main meal) to regular insulin therapy 1) improve postprandial glycaemic excursions and 2) provide improved, long-term glycaemic control measured as HbA1c and glycaemic variability?

During the study, a physician will follow each participant with careful evaluation of insulin treatment with glycaemic optimization and study-drug safety and efficacy. This is expected to lower the adverse-event risk. Exenatide is approved for the treatment of type 2 diabetes by the European Medicines Agency and by the US Food and Drug Administration. Prior studies have shown limited side effects such as nausea, vomiting, hypoglycaemia and headache. Nausea and vomiting, generally transient, usually occur within three weeks after treatment initiation. They can be minimized by gradual dose titration, as planned in this study. The hypoglycaemia risk is reduced by insulin-dose reduction at study start and by instructing participants in careful blood glucose monitoring. Few cases of acute pancreatitis have been reported in persons with type 2 diabetes using exenatide, but the incidence was similar to the type-2-diabetes background population. Overall, the risk of side effects in this study is expected to be modest. Arginine injection is a well-validated, safe method to evaluate pancreatic alpha and beta cell function, but potentially associated with transient mild flushing, nausea and metallic taste. Vein puncture may cause a short pain, risk of a small haematoma and a minimal risk of puncture-site infection. In total, 400 ml blood and 80 ml of urine per person will be collected throughout the study. At the two DXA scans, participants will be exposed to weak X-ray radiation (less than 1 mSv in total). For comparison, the background radiation in Denmark is about 3 mSv per year. The risk of complications, or adverse events, is negligible for all other planned study procedures.

Data will be processed and merged into one or more scientific articles and published in accordance with the CONSORT 2010 statement in international, peer-reviewed scientific journals and presented at national and international scientific meetings. Positive, negative and inconclusive results together with statistical method will be published as soon as scientifically justifiable. AstraZeneca commented on the study design but will have no influence on trial conduction, data analysis, interpretation or publication. All data are owned by the authors, who all have full data access.

Study approval

The MAG1C trial is approved by the Danish Medicines Authority (Eudract-nr.: 2016-001365-92), the Regional Scientific-Ethics Committee of the Capital Region of Denmark (H-16034515) and the Data Protection Agency (2012-58-0004) with a current, approved (15 February 2018) study protocol version 1.6. It is registered at ClinicalTrials.gov (NCT03017352). The study will be conducted under the surveillance and guidance of the Good clinical practice (GCP) unit at Copenhagen University Hospital Bispebjerg in accordance with the ICH-GCP guidelines and the Helsinki Declaration. The study commenced in January 2017 and is expected to be reported in 2019. Presently (May 2018), 58 study participants have been included in the MAG1C study.

AUTHOR'S CONTRIBUTIONS

NJJ, TFD, AL, TV, HUA and FKK conceived and designed the study. FKK is guarantor of the study and sponsors the trial. NJJ drafted the manuscript and all authors have contributed to the revision of the manuscript and read and approved the final version of the manuscript.

COMPETING INTERESTS STATEMENT

NJJ and TV have no competing interests. TFD has received research support from Novo Nordisk and AstraZeneca, and has received lecture fees from Novo Nordisk. AL has received lecture fees from Novo Nordisk, Boehringer Ingelheim and Eli Lilly. HUA owns stocks in Novo Nordisk and serves in advisory boards for Novo Nordisk and Astra Zeneca. FKK has served on scientific advisory panels and/or speaker's bureaus for, served as a consultant to and/or received research support from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Gubra, MSD/Merck, Novo Nordisk, Sanofi and Zealand Pharma.

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Figure 1. Flowchart

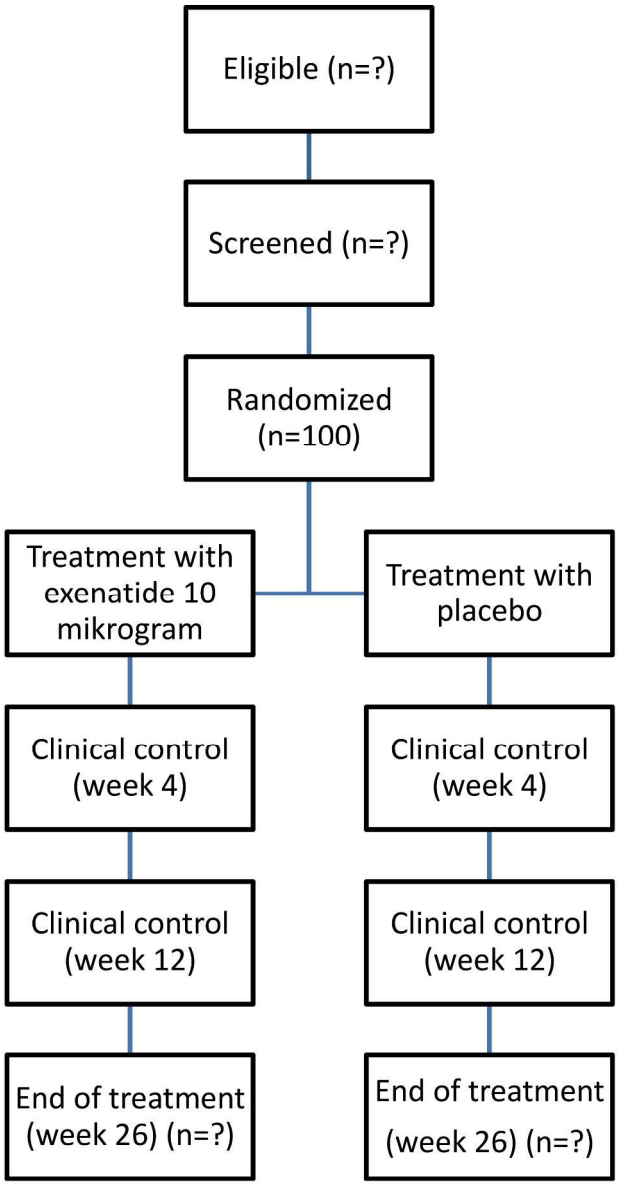

Figure 1: Flowchart

178x337mm (300 x 300 DPI)

SPIRIT 2013 checklist for the MAG1C trial protocol article
Version 1.0, 7 May 2018

Administrative information

1
All requested information is included in the title.

2a
Please refer to the abstract and *Ethics and dissemination* section under the *Study approval*, page 17.

2b
NA.

3
Please refer to the *Ethics and dissemination* section under *Study approval*, page 17.

4
Please refer to the Funding statement section, page 17.

5a
Please refer to the *Author's contributions* section, page 17.

5b
Please refer to page 1.

5c
Please refer to the *Ethics and dissemination* section, page 16.

5d
Not relevant.

Introduction

6a
Please refer to the *Introduction section, page 4.*

6b
Please refer to the *Introduction section, page 4.*

7
Please refer to the *Introduction section* under *Hypothesis* and *Objectives and endpoints, page 5.*

8
Please refer to the *Introduction section* under *Trial design, page 8.*

Methods: Participants, interventions, and outcomes

9
Please refer to the *Methods and analysis section*, page 8. The study only study site is Steno Diabetes Center Copenhagen, so no study site list is provided.

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10
Please refer to *Table 2. Eligibility criteria*, page 9.

11a
Please refer to the *Intervention* section, page15.

11b
Please refer to *Table 2. Eligibility criteria* under *Withdrawal criteria*, page 9.

11c
Please refer to the *Methods and analysis section* under *Trial visits and examinations*, page 10.

11d
Please refer to the *Methods and analysis section* under *Trial visits and examinations*, page 10.

12
Please refer to *Table 1. Primary and secondary endpoints*, page 7.

13
Please refer to *Table 4. Trial outline*, page 13 –14.

14
Please refer to the *Methods and analysis section* under *Data analysis*, page 15 –16.

15
Please refer to the *Methods and analysis section* under *Study population*, page 8.

Methods: Assignment of interventions (for controlled trials)

16a
Please refer to the *Methods and analysis section*, page 8.

16b
Please refer to the *Methods and analysis section*, page 8.

16c
Please refer to the *Methods and analysis section*, page 8 and under *Trial visits and examinations*, page 10.

17a
As a double-blinded study, both investigators and study participants are blinded until last patient last visit. Further, the investigators will be blinded during the data analysis. Please refer to the *Introduction section* under *Trial design, page 8 and Methods and analysis section* under *Data analysis*, page 15

17b
Please refer to the *Methods and analysis section*, page 7.

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Methods: Data collection, management, and analysis

18a
Please refer to the *Methods and analysis section* under *Trial visits and examinations*, page 10 and *Table 4. Trial outline*, page 13 –14.

18b
Please refer to the *Methods and analysis section* under *Trial visits and examinations*, page 10; *Table 4. Trial outline*, page 13 –14 and *Methods and analysis section* under *Data analysis*, page 15.

19
Please refer to the *Methods and analysis section*, page 8.

20a
Please refer to the *Methods and analysis section* under *Data analysis*, page 15.

20b
Please refer to the *Methods and analysis section* under *Data analysis*, page 15.

20c
Please refer to the *Methods and analysis section* under *Data analysis*, page 15.

Methods: Monitoring

21a
Please refer to the *Ethics and dissemination* section under the *Study approval*, page 17.

21b
NA.

22
Please refer to the *Methods and analysis section* under *Trial visits and examinations*, page 10.

23
Please refer to the *Ethics and dissemination* section under the *Study approval*, page 17.

Ethics and dissemination

24
Please refer to the *Ethics and dissemination* section under the *Study approval*, page 17.

25
Please refer to the *Ethics and dissemination* section under the *Study approval*, page 17.

26a
Please refer to the *Methods and analysis section* under *Trial visits and examinations*, page 10.

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26b
A substudy on the role of the microbial gut flora has been approved by the Danish regulatory authorities. It involves collection of faecal specimens at each study visit. It is voluntarily to participate. A decline does not affect participation in the MAG1C study. Please refer to the *Methods and analysis section* under *Trial visits and examinations*, page 10.

27
All data are pseudo anonymised. Please refer to the *Methods and analysis section*, page 8.

28
Please refer to the *Competing interests statement section*, page 17.

29
Please refer to the *Ethics and dissemination* section, page 16.

30
Not relevant.

31a
Please refer to the *Ethics and dissemination* section, page 16.

31b
Please refer to the *Ethics and dissemination* section, page 16.

31c
NA.

Appendices

32
Please see the attached appendix with the written informed consent form for the MAG1C trial as well as substudy mentioned under 26b.

33
Please refer to *Table 4. Trial outline*, page 13 –14.