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Study protocol for a randomised, double-blind, placebo-controlled crossover trial assessing the impact of the SGLT2 inhibitor empagliflozin on postprandial hypoglycaemia after gastric bypass

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ABSTRACT

Introduction Postprandial hypoglycaemia after gastric bypass surgery (also known as postbariatric hypoglycaemia or PBH) is an increasingly encountered clinical problem. PBH is characterised by meal-induced rapid spikes and consequent falls in glycaemia, resulting in both hypoglycaemia burden and high glycaemic variability. Despite its frequency, there is currently no approved pharmacotherapy. The purpose of this investigation is to evaluate efficacy and safety of empagliflozin 25 mg, a sodium-glucose cotransporter 2-inhibitor, to reduce glucose excursions and hypoglycaemia burden in patients with PBH after gastric bypass surgery.

Methods and analysis In a prospective, single-centre, randomised, double-blind, placebo-controlled, crossover trial, we plan to enrol 22 adults (≥18 years) with PBH after Roux-en-Y gastric bypass surgery (plasma or sensor glucose <3.0 mmol/L). Eligible patients will be randomised to receive empagliflozin 25 mg and placebo once daily, each for 20 days, in random order. Study periods will be separated by a 2–6 weeks wash-out period. The primary efficacy outcome will be the amplitude of plasma glucose excursion (peak to nadir) during a mixed meal tolerance test. Results will be presented as paired-differences±SD plus 95% CIs with p values and hypothesis testing for primary and secondary outcomes according to intention-to-treat. Secondary outcomes include continuous glucose monitoring-based outcomes, further metabolic measures and safety.

Ethics and dissemination The DEEP-EMPA trial (original protocol title: Randomized, double-blind, placebo-controlled crossover trialassessing the impact of the SGLT2 inhibitor empagliflozin onpostprandial hypoglycaemia after gastric bypass) was approved by the Bern Ethics Committee (ID 2021-01187) and Swissmedic (Ref. Number: 102663190) in October and November 2021, respectively. First results are expected in the first quarter of 2023 and will be disseminated via peer-reviewed publications and presented at national and international conferences. The acronym DEEP was derived from an overarching project title (DEciphering the Enigma of Postprandial Hyperinsulinaemic Hypoglycaemia after Bariatric Surgery), the term EMPA stands for the drug empagliflozin.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ First study that investigates the effect of empagliflozin 25mg on glycaemic variability and hypoglycaemia burden in patients with postbariatric hypoglycaemia.
⇒ Randomised, double-blind, placebo-controlled, crossover study design.
⇒ Preliminary data will be key to establish the relevance for larger and longer trials assessing the efficacy of empagliflozin 25 mg in reducing postbariatric hypoglycaemia in unrestricted daily living.
⇒ Single-site design and short time-frame may limit applicability of findings to different contexts.

Trial registration number NCT05057819.

INTRODUCTION

Bariatric surgery is an increasingly used anti-obesity treatment demonstrating sustained weight loss, remission of type 2 diabetes, reduction of cardiovascular events, cancer and all-cause mortality.[1 2]

However, adverse effects can occur such as the increasingly recognised late metabolic complication known as postbariatric hypoglycaemia (PBH). The condition develops one to several years after bariatric surgery, mainly Roux-en-Y gastric bypass (RYGB). Prevalence estimates range widely due to differing diagnostic criteria used and high prevalence of asymptomatic patients.[3 4] Recent work suggests that the occurrence of PBH may be as high as 30% of patients undergoing RYGB.[5 6] The complication is also observed in patients with type 2 diabetes before surgery, independently of its remission.[7] PBH manifests 1–3 hours

after meals[8] and may be accompanied by neuroglycopenic symptoms, but their sensitivity has recently reported to be poor.[9] In affected patients, the toll on quality of life can be profound and in a recently published study, the proportion of individuals with a history of PBH-induced loss of consciousness or hospitalisation was 50%.[9] While the underlying physiology is incompletely understood, inappropriately high postprandial insulin exposure, caused by both accelerated glucose absorption from the gut and increased insulinotropic hormones such as GLP-1, are well established.[10] Additional factors such as diminished insulin clearance, alterations in postprandial bile acid kinetics, and blunted neuro-endocrine counter-regulation may be further contributors.[11–14]

In the absence of approved pharmacotherapies for PBH, dietary modification, mainly carbohydrate restriction is first-line therapy.[15] Second-line approaches include off-label use of acarbose and other systemic acting drugs such as somatostatin analogues, diazoxide and/or calcium channel blockers. The use of these medications is limited by poor tolerability, inconvenient mode of administration, high costs or restricted availability (eg, acarbose no longer available on the Swiss market).[8 16]

In a proof-of-concept study, a single dose of 10 mg empagliflozin was administered to 12 patients with PBH and significantly lowered the proportion of patients experiencing hypoglycaemia during a standardised mixed meal tolerance test compared with placebo (2 vs 7 translating into a 74% risk reduction).[17] Empagliflozin is an inhibitor of the sodium-glucose cotransporter 2 (SGLT2)[18] that resides in the brush border membrane of proximal tubular cells in the kidney and reabsorbs ~90% of glucose filtered at the glomerulus.[19] Empagliflozin blocks the physiological glucose reabsorption in the proximal tubule from the glomerular filtrate, thereby reducing postprandial hyperglycaemia through increased urinary glucose excretion. A dose-dependent increase in urinary glucose excretion and reduction of plasma glycaemic exposure was observed.[20 21] Inhibition of SGLT2 with empagliflozin and other SGLT2 inhibitors were also shown to stimulate endogenous glucose production, which was accompanied by an increase in plasma glucagon levels.[22–24]

Empagliflozin 10 mg or 25 mg once daily is approved for the treatment of type 2 diabetes and was also shown to exert cardiovascular and renal protection, independent of its glucose-lowering effect.[20 25 26]

As far as safety is concerned, therapy with SGLT2 inhibitors is generally well tolerated. An increased incidence of genital infections and (although rare) euglycaemic ketoacidosis are known side effects. The latter is mainly observed in patients with type 1 diabetes and less frequently in those with type 2 diabetes.[18] No cases of euglycaemic ketoacidosis in individuals without diabetes treated with SGLT2 inhibitors have been reported.

Taken together, the pharmacodynamic profile of empagliflozin and the preliminary data in the PBH patients suggest that SGLT2 inhibitors could effectively reduce glycaemic variability and hypoglycaemia burden in this population while showing high tolerability and convenience of administration.

METHODS AND DESIGN

Study objectives

Overall objective

The overall objective of the DEEP-EMPA trial is to evaluate whether empagliflozin 25 mg has therapeutic potential to lower the burden of PBH.

Primary objective

To assess the efficacy of empagliflozin 25 mg in reducing glucose excursions in individuals with PBH.

Secondary objectives

To determine the efficacy of empagliflozin 25 mg to reduce glycaemic variability and burden of hypoglycaemia.

Further objectives

To determine the impact of empagliflozin 25 mg on glucose-insulin homoeostasis.

To determine the effect of empagliflozin 25 mg on fasting and postprandial glucagon levels.

To assess the effect of empagliflozin 25 mg on ketone levels.

To assess carbohydrate-based meal patterning while taking empagliflozin 25 mg.

Safety objectives

Even though the small sample size does not allow for a conclusive safety profiling, adjudicate adverse events of special interest and serious adverse events will be collected and analysed.

Study outcomes

Primary outcome

The primary outcome will be addressed by evaluating the amplitude of the decrease in plasma glucose (difference between peak and nadir plasma glucose concentration in mmol/L) during the mixed meal test. Plasma glucose will be quantified using a point-of-care glucose analyser (Accu-Chek Inform II, Roche Diagnostics). The outcome will be assessed during the mixed meal test on the day of the experimental visit at the end of each study period.

Secondary outcomes

The following variables will be assessed to address the effect on glucose excursions:

- Mean amplitude of glucose excursion (MAGE) based on sensor glucose. The MAGE will be calculated based on CGM data (Dexcom G6). Calculations will be performed in R using the software package iglu.[27]
  - The outcome will be calculated from day 1 (start of IMP/Placebo intake) to the end of the respective period (day 20-24) of intake of investigational medicinal product (IMP)/placebo (ie, aggregated measures of the outcome will be calculated for

each period). The first 3 days of data of each period will be discarded.

- Peak plasma glucose during the mixed meal test
  - The outcome will be assessed during the mixed meal test on the day of the experimental visit at the end of each study period (day 20–24 of the respective study period).
- Percent time spent with sensor glucose>10.0 mmol/L
  - The outcome will be calculated from day 1 (start of IMP/Placebo intake) to the end of the respective period (day 20-24) of intake of IMP/placebo (ie, aggregated measures of the outcome will be calculated for each period). The first 3 days of data of each period will be discarded.

The following variables will be assessed to address the effect on glucose variability:

- Mean coefficient of variability based on sensor glucose
  - The outcome will be calculated from day 1 (start of IMP/Placebo intake) to the end of the respective period (day 20-24) of intake of IMP/placebo (ie, aggregated measures of the outcome will be calculated for each period). The first 3 days of data of each period will be discarded.

The following variables will be assessed to address the effect on hypoglycaemia:

- Proportion of participants experiencing hypoglycaemia (defined as plasma glucose <3.0 mmol/L) during the mixed meal tolerance test.
  - The outcome will be assessed during the mixed meal test on the day of the experimental visit at the end of each study period (day 20–24 of the respective study period).
- Nadir plasma glucose during the mixed meal test
  - The outcome will be assessed during the mixed meal test on the day of the experimental visit at the end of each study period (day 20–24 of the respective study period).
- Percent time spent with sensor glucose<3.0 mmol/L
  - The outcome will be calculated from day 1 (start of IMP/Placebo intake) to the end of the respective period (day 20-24) of intake of IMP/placebo (ie, aggregated measures of the outcome will be calculated for each period). The first 3 days of data of each period will be discarded.
- Percent time spent with sensor glucose <2.8 mmol/L (in accordance with a recently published International consensus on the diagnosis of PBH).[28]
  - The outcome will be calculated from day 1 (start of IMP/Placebo intake) to the end of the respective period (day 20-24) of intake of IMP/placebo (ie, aggregated measures of the outcome will be calculated for each period). The first 3 days of data of each period will be discarded.
- Frequency of postprandial symptoms based on a modified Edinburgh Hypoglycaemia Symptom Scale
  - The outcome will be calculated from day 1 (start of IMP/Placebo intake) to the end of the respective period (day 20-24) of intake of IMP/placebo.

Exploratory outcomes

- Insulin response during the mixed meal test (incremental area under the curve (AUC) from 0 to 120 min following meal ingestion).
  - The outcome will be assessed during the mixed meal test on the day of the experimental visit at the end of each study period (day 20–24 of the respective study period).
- Measures of beta-cell function, insulin sensitivity and first-pass hepatic insulin extraction using the oral minimal model method[29 30] calculated using data from the mixed meal test.
  - The outcome will be assessed during the mixed meal test on the day of the experimental visit at the end of each study period (day 20–24 of the respective study period).
- Total amount of daily excreted glucose (g/24 hours) measured in the 24 hours urine collection.
  - The outcome will be assessed during the day before the experimental visit.
- Glucagon response during the mixed meal test (incremental AUC from 0 to 120 min following meal ingestion).
  - The outcome will be assessed during the mixed meal test on the day of the experimental visit at the end of each study period (day 20–24 of the respective study period).
- Ketone levels (3-beta-hydroxybutyrate) during the mixed meal test.
  - The outcome will be assessed during the mixed meal test on the day of the experimental visit at the end of each study period (day 20–24 of the respective study period).
- Average daily meal frequency (carbohydrate content ≥30 g/24 hours and <30 g/24 hours) assessed during the treatment periods.
  - The outcome will be calculated from day 1 to day 20 of intake of IMP/placebo.

Safety outcomes

Safety endpoints to be analysed include a descriptive summary of the following parameters:

- Serious adverse events.
- Adverse events of special interest.
- Vital signs.

Assessment of outcomes

- The primary outcome will be assessed during a standardised mixed meal tolerance test at the end of each study period (visit 1 and 2).
- Secondary outcomes will be assessed at visit 1 and 2 (mixed meal tolerance test) and during daily living using continuous glucose monitoring (CGM). Outcomes based on sensor glucose will be calculated from the fourth day following start of the IMP/placebo intake until the end of the respective period.
- Further outcomes will be assessed during visit 1 and 2 (mixed meal tolerance test) and during daily living

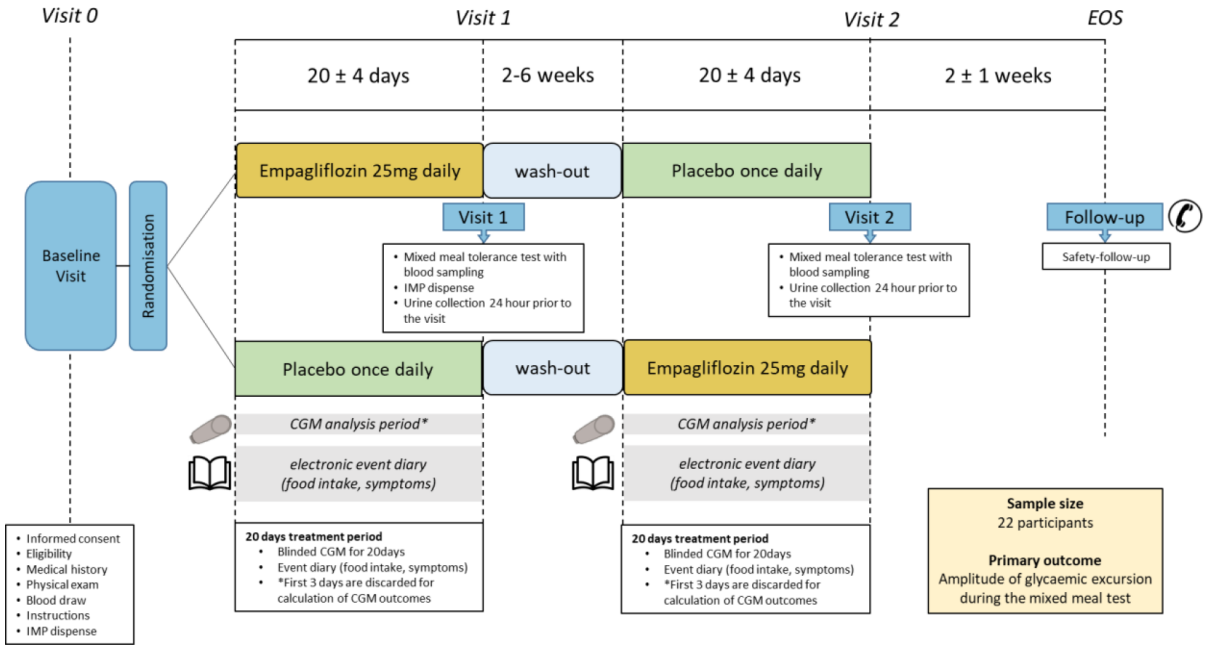

Figure 1 The DEEP-EMPA trial study design. CGM, continuous glucose monitoring; EOS, end of study visit; IMP, investigational medicinal product.

using records of symptoms and nutritional intake. Logging of symptoms and nutritional intake will be done using an electronic diary.

Study design

The DEEP-EMPA trial is an investigator-initiated randomised, double-blind, placebo-controlled, cross-over, single-centre study. Twenty-two participants will be randomised in equal proportions into two groups (11 participants per group). In one group, 25 mg once daily empagliflozin, the IMP, will be given as the first treatment, and a placebo in a form identical to empagliflozin as the second treatment. The other group receives the same treatments in the reverse sequence. Study duration will be 2×20 days with a randomised crossover allocation and an interspersed wash-out period of 2–6 weeks (figure 1). Empagliflozin (instead of alternative SGLT-inhibitors) was chosen due to the already existing preliminary findings in PBH patients[17] and the almost exclusive selectivity for the renal SGLT2 over the intestinal SGLT1 allowing to assign potential drug effects to a specific target. The rationale for the 25 mg dose was the previously shown higher potency to induce glucosuria and reduce hyperglycaemia.[20 21]

Study population

Eligible population consists of post-bariatric surgery patients, 18 years or older, who underwent RYGB ≥1 year ago, and with biochemically confirmed postprandial hypoglycaemia defined as plasma or sensor glucose measurement of <3.0 mmol/L within the last 3 months before recruitment. This threshold has been recognised by the International Hypoglycaemia Study Group as clinically important hypoglycaemia due to its association with neuroglycopenic symptoms and adverse health effects.[31] Based on findings of a recent study, the threshold of 3.0 mmol/L irrespective of the presence of neuroglycopenic symptoms was proposed to signify clinically important hypoglycaemia specifically in the PBH population.[9] Recruitment occurs via local advertisements and referrals from internal and external bariatric physicians. Written informed consent will be obtained before any study-related procedures (the patient consent form is included in online supplemental appendix). Study participation will be reimbursed for their efforts and time (CHF 300 plus study-related travel costs).

Exclusion criteria

- Diabetes on antidiabetic treatment (insulin and/or non-insulin agents).
- Chronic kidney disease (defined as Chronic Kidney Disease Epidemiology Collaboration estimated glomerular filtration rate <60 mL/min/1.73 m^2 body surface area).
- Genito-urinary infection, if not treated successfully.
- Pregnant and lactating women (urine pregnancy test to be performed for women of childbearing potential (defined as women who are not surgically sterilised/hysterectomised and/ or who are postmenopausal for less than 12 months)) or women of childbearing potential that refuse to use an effective contraceptive method (birth control pill or intrauterine contraceptive device)).
- Inability to understand and follow the protocol.
- Known allergy to the study drug.
- Participation in another interventional clinical trial overlapping with the current trial.

Randomisation

The randomisation to the treatment sequence will be performed by the principle of simple randomisation using a computer-generated sequence. The randomisation list will be generated by the Scientific Officer (SO) of the Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism of the University Hospital Bern, otherwise not involved in the trial with no access for persons directly involved in the trial.

Study procedures

Eligible individuals will be randomised in equal proportions to 20 days 25 mg empagliflozin followed by 20 days of placebo or vice-versa, taken once daily per os in the morning. Placebo will be administered in a form identical to empagliflozin. Before randomisation, participants will attend a baseline visit (see figure 1). Participants will remain on the assigned IMP/placebo for 20±4 days. On the last day of each period, participants will perform a 24 hours urine collection. Instructions for the urine collection will be given at the time of the baseline visit and participants will be reminded by an email or phone call immediately prior to the collection period. On day 20, participants will attend the clinical research facility to undergo a standardised mixed meal tolerance consisting of a breakfast roll with butter and jam, combined with a fruit yoghurt (584 kcal, 85 g of carbohydrates, 21 g of fat and 12 g of protein). Participants will be asked to ingest the meal within 15 min in an upright position. Frequent blood sampling for plasma glucose (Accu-Chek Inform II, Roche Diagnostics), insulin, C-peptide and glucagon (immunometric assays by Roche, Siemens and Mercodia) at baseline and 10 min, 20 min, 30 min, 60 min, 90 min, 120 min, 135 min, 150 min following mixed meal ingestion will be performed. Additionally, ketone levels (3-beta-hydroxybutyrate) will be assessed at baseline and 30 min, 60 min following mixed meal ingestion using a point-of-care device (FreeStyle Precision Neo, Abbott) to inform about potential effects of empagliflozin on fasting ketogenesis due to the known shift to fatty substrate utilisation as well as the extent of the suppressive effect of postprandial insulin.[32] The two study periods will be separated by a wash-out period of 2–6 weeks. During the two 20 days periods, participants will be fitted with a blinded continuous glucose monitor (Dexcom G6) and record symptoms and carbohydrate intake (semiquantitative, eg, ≥30 vs <30 g, according to nutritional guidelines for the management of PBH[15]) in an electronic diary. The same diary will be also used to monitor adherence to IMP/placebo. Two weeks after completion of the second treatment, participants will receive a phone call to inquire about a general well-being and safety events.

Statistical methods

Sample size

The sample size was calculated based on the primary outcome. In a preliminary study involving a sample of 12 patients with PBH, the mean paired-difference (empagliflozin−placebo) of the decrease in plasma glucose following a mixed meal test was −1.46 mmol/L (SD 0.31 mmol/L). With a sample size of 17 participants, the study would detect a mean paired-difference of 0.3 mmol/L (this corresponds to an effect size of 0.75 with the assumption of a within participant SD of 0.35 mmol/L) with a power of 90% at a 5% alpha-level using a two-tailed test. To allow for 20% dropouts, a sample size of 22 will be recruited. The power calculation was carried out using G*Power (V.3.1).

Hypothesis

The null hypothesis is that there is no difference in the amplitude of the decrease in plasma glucose during the mixed meal test with empagliflozin compared with placebo. The alternative hypothesis is that there is a significant difference between empagliflozin and placebo in the amplitude of plasma glucose decrease (two-sided alternative).

Statistical analysis

The statistical analysis of the trial will be done by a statistician blinded to the allocated sequence in accordance with a statistical analysis plan. The plan describes all necessary data preparation steps (eg, additional validations, generation of new variables), definitions (eg, analysis sets) and statistical analyses (eg, models, outputs such as tables and graphs). Results from statistical analyses will be presented as effect measures plus 95% CIs. Analysis of the primary and secondary outcomes will be accompanied by p values and hypothesis testing with a significance level of 0.05 using two-sided tests.

The main analyses will be done based on an intention-to-treat basis, whereby all randomised participants will be analysed in the allocated group regardless of any protocol violations such as cross-overs (which can only happen accidentally in this trial), subjects that did not receive the treatment in the randomised sequence or subjects that did not comply with the intervention. A sensitivity analysis, done based on the per-protocol basis, will be performed including only participants compliant to the IMP intake. Non-compliance is defined as: in any of the two treatment periods, (1) more than two non-consecutive days with missed intake of the allocated capsule; or (2) more than four missed tablets (ie, to be compliant, patients must take at least 16 tablets); or (3) missed intake on the day of visit 1 or 2.

Primary analysis

Linear mixed effects model will be used for the statistical analysis. The mixed effects model will contain the treatment and period as fixed effects to adjust for any period effects, and a random effect for participants to account for within-participant correlation of repeated measurements. Residual values will be assessed for normality using the Shapiro-Wilk test. Transformations to normality for variables not fulfilling normality assumptions will be considered (eg, log, Box-Cox, etc). All primary and secondary

endpoints will be analysed using this approach. We will notably not formally test for possible carry-over effects due to the long wash-out period and to avoid any inflation of type I error. Mean±SD or summary statistics appropriate to the variable type will be reported for the primary and secondary efficacy outcomes for the two treatments. Results from statistical analyses will be presented as paired-differences±SD along with 95% CIs. A two-sided p value will be reported and a p value <0.05 will be considered statistically significant.

Statistical interim analysis

No interim analysis is planned.

Safety analysis

A descriptive summary of safety events will be tabulated for each treatment. No formal statistical testing will be applied. Safety outcomes entail the following:

- Serious adverse events.
- Adverse events of special interest.
- Vital signs.

Quality assurance and control

Monitoring

For quality control of study conduct and data retrieval, the study site will be visited by appropriately trained and qualified monitors. All source data and relevant documents will be accessible to monitors and questions of monitors are answered during site visits. Any findings and comments will be documented in site visit reports and communicated to the responsible stakeholders. All monitoring activities will be defined in a monitoring plan prior to study start (first participant enrolled).

Data management

The Case Report Forms are implemented electronically using the study database REDCap. REDCap supports data analysis by integrated tools for creating reports and charts.[33 34] All data will be exported in a CSV format and transferred to the statistical software package for analysis. All data will be archived and secured in the database for at least 10 years.

Patient and public involvement

Patient experiences were considered for the design of the study, including the choice of outcomes. In the informed consent form, patients agree for findings to be disseminated in peer-reviewed journal and conferences. Findings will also be presented at patient education and support events.

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Contributors LB is the sponsor-investigator of the trial and procured funding. LB and DH conceived the study. LB, DH and AM wrote the study protocol and registered the study. AFacchinetti and CDM were involved in development of the methodology and data analysis plan. LB, DH and CTN wrote the statistical analysis plan. LB, DH and AFerreira coordinate the study. LB and AFerreira are involved in the recruitment of patients and patient care. APV is involved in patient care. LB, AFerreira, AE drafted the first protocol manuscript. All authors contributed to the manuscript and all authors read and approved the final version.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

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Request to participate in medical research:

Effect of empagliflozin on hypoglycaemia after gastric bypass surgery - a randomised-controlled double-blind study

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Dear Madam, Dear Sir

We hereby ask you if you would be willing to participate in our research project.

Your participation is voluntary. All data collected in this project are subject to strict data protection regulations. The research project is being conducted by the University Clinic for Diabetes, Endocrinology, Nutritional Medicine and Metabolism at the Inselspital Bern. If you are interested, we would be happy to keep you informed as to the project findings.

We will explain the most important points to you and answer your questions. In this first section you will find the most important points briefly summarized. In the following section, these points will be covered in more detail.

Why are we conducting this research project?

- Recurrent hypoglycaemia after eating can occur as an undesirable late effect of weight-reducing surgery, especially gastric bypass surgery.
- Currently, there is no approved drug to treat this undesirable late effect.
- A drug that was used in the past is no longer available in Switzerland and was often not tolerated due to side effects.
- Initial research results show that the active pharmaceutical agent empagliflozin, which is normally used for diabetes, can reduce the discomfort of hypoglycaemia after gastric bypass surgery.
- In our research project, we are investigating the effectiveness of empagliflozin against hypoglycaemia after gastric bypass surgery for 20 days.

What do I have to do when I participate? - What happens to me when I participate?

- If you decide to take part, you will take the drug empagliflozin and a placebo (a similar-looking tablet without the active ingredient) for 20 days each. The order will

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be randomised and neither you nor the healthcare professional will know whether you are taking the drug or the placebo (double blinding).

- At the beginning, we will check your eligibility to take part in the study, inform you about the study procedure and obtain your written consent. You will then receive the first dose of the medication (empagliflozin or placebo).
- After 20 days you will have breakfast with us. We will take blood before and after this to measure blood sugar and hormones. This visit lasts about 3 hours.
- After a break of 2-6 weeks you will receive the second medication. After another 20 days, we will carry out the same test with breakfast and regular blood sampling at the hospital (duration again approx. 3 hours).
- While taking the medication, your sugar history is recorded with a device that is worn on the skin. You will need to document the time of your meals and any complaints electronically.

What are the benefits and risks involved?

Benefit

- With your participation you will contribute to the availability of new treatment options for hypoglycaemia after gastric bypass surgery.
- By participating, you will help future patients.

Risk and burden

- Empagliflozin is approved for the treatment of diabetes and has a very favourable tolerability profile.
- In people with diabetes, the most common side effects are increased urination and urinary tract infections.

By signing at the end of the document, you confirm that you are voluntarily participating in the study and that you have understood the contents of the entire document.

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Detailed information

1. Aim and selection

We refer to our research project as a *study* in this information letter. If you participate in this study, you are a *study participant*.

Before a drug is used for a disease, it must be scientifically tested in study participants. The aim of this study is to investigate the benefit of a new treatment in people who suffer from hypoglycaemia after eating (so-called "postprandial hypoglycaemia") as a result of gastric bypass surgery.
The drug in question is the drug Jardiance® (active ingredient: empagliflozin). (active ingredient: empagliflozin), which is currently approved in Switzerland for the treatment of patients with diabetes. Data from a recently published study by researchers at the University of Basel suggest that taking empagliflozin in the daily lives of patients who have undergone gastric bypass surgery can reduce blood sugar fluctuations and the occurrence of hypoglycaemia after meals. Empagliflozin inhibits the reuptake of sugar in the kidneys and thus reduces the rise in blood sugar after eating sugary meals. The lower rise in blood sugar means that less insulin (blood sugar-lowering hormone) is released, which reduces the risk of hypoglycaemia and blood sugar fluctuations. In the study, we use the approved dose of 25 mg per day for diabetes patients. In healthy people, doses of up to 800 mg per day have been tested without any safety problems.

We are inviting you to participate because you suffer from hypoglycaemia after eating, have had gastric bypass surgery more than one year ago and are older than 18 years. People who are not suitable to take empagliflozin (at the discretion of the investigator) are excluded from participation. Other exclusion criteria include complicated urinary tract infections, renal impairment, current or planned pregnancy, and breastfeeding or taking medications that affect blood glucose during the study period.

2. General information

- This project is being carried out with a total of 22 adults at the Inselspital Bern.
  It will be decided at random (so-called randomisation) whether you will be treated first with empagliflozin 25 mg or placebo (the same-looking tablet without active ingredient), or vice versa. All participants will receive both treatments: half will start with empagliflozin and then receive placebo, and the other half will be treated in the reverse order. Neither you nor your healthcare team will know the group allocation (called double blinding). Only the placebo control can determine whether there are differences between the spontaneous course and the treatment with empagliflozin. Both tablets (empagliflozin and placebo) are taken once a day for 20 days each, with a break of 2-6 weeks.
- The response to the therapy is examined with a meal test at our clinic on day 20 of each treatment phase. You will be given breakfast. Before and after this, regular blood samples will be taken. During each treatment phase, you will also wear a continuous glucose meter on your skin and record your meal intake and any symptoms electronically. On day 19 of each treatment phase, you will also have to do a 24-hour urine collection.
- Empagliflozin is approved in Switzerland for the treatment of diabetes. Because of its mode of action, it is thought that empagliflozin may also be effective for hypoglycaemia after ingestion of meals following, for example, gastric bypass surgery. Empagliflozin also has a good safety profile in people without diabetes.
- The study will be conducted as required by the laws in Switzerland. In addition, we will observe all internationally recognised guidelines. The responsible cantonal ethics committee and Swissmedic have reviewed and approved the study. A description of this study can also be found on the website of the Federal Office of Public Health: www.kofam.ch.

3. Procedure

The procedure for participating in the study is shown in Figure 1.
At your first visit (visit 0), we will check your suitability for the study, clarify any questions and - if you wish to participate in this study - obtain your written consent. If you are taking medication that affects blood sugar but want to take part in the study, this medication will be stopped for a certain period of time. Your investigator will explain this to you. We will give you the first bottle of medication (either empagliflozin or placebo) and explain how to wear the continuous glucose monitor, how to record meals and complaints electronically and the 24-hour urine collection before the second visit (visit 1). You will now take one tablet of the medicine every day in the morning. On the 19th day you will start collecting your urine for 24 hours. On the 20th day of taking the medicine, you will arrive at our clinic in a fasted state for visit 1. You will have breakfast with us. We will take blood before and after this to measure the sugar in your blood and hormones that affect blood sugar. We will take 75ml of blood per test, which is not problematic for your health (comparison: 450-500ml of blood is taken during a blood donation). The test takes about 3 hours. In the collected urine, which you bring with you to the visit, we measure the excretion of sugar via the kidneys. The continuous glucose measurement and the recording of meals and complaints are used to evaluate the blood sugar fluctuations and complaints while taking the medication. At the end of visit 1, you will receive the 2nd bottle of medication (either empagliflozin or placebo). After a break of 2-6 weeks, you will again take one tablet of the drug daily in the morning for 20 days. On day 20, you will attend our clinic for visit 2. You will carry out the continuous glucose measurement, recording of meals and complaints, and urine collection on day 19 of tablet intake without any changes. The procedure for visit 2 is exactly the same as that for visit 1.
After visit 2, the treatment of the study ends. After 2 weeks you will be interviewed by telephone about your state of health.

In certain cases, we may have to exclude you from the study prematurely. This may happen if you have circumstances that prohibit further participation in the study, or if the investigator is of the opinion that further participation in the study would endanger your health. In this case, for your safety, you will be contacted after 2 weeks and, if necessary, examined at our clinic. Please bring all medication and materials we have given you back to us. Your family doctor will be informed about your participation in the study.

4. Benefit

Through this study, we will gain important insights into new treatment options for postprandial hypoglycaemia after gastric bypass surgery. These results will be of benefit to other people who have similar complaints.

5. Voluntary participation and obligations

Participation is voluntary. If you do not want to participate in this study or decide during participation that you would like to withdraw, you do not have to justify this. Your medical treatment/care is guaranteed regardless of your decision.

If you participate in the study, you must follow certain rules. This is necessary for your health and safety. We will support you as best we can. As a study participant, you are obliged to,

- follow the medical instructions of your investigator(s) and adhere to the study plan.
- come to visits 1 and 2 on an empty stomach (i.e. not having eaten anything since midnight and only having drank water if necessary). You can also take the medication on the days of visits 1 and 2 in the morning with a sip of water. This also applies to any other medication you may be taking.
- to bring the bottle of medication with you on visits 1 and 2.

- inform your investigator about any changes in your state of health. In particular, also report new symptoms, new complaints and changes in your state of health (also after the end of the study/discontinuation, e.g. until the adverse effect subsides);
- discuss with your investigator any concurrent treatments or therapies you wish to receive from another doctor while participating in the study; and
- Always inform your investigator about any additional medication you are taking. Please list all medicines, including those you have bought yourself, for which you do not need a prescription or alternative medicine preparations.

6. Risks and burdens

Empagliflozin has been shown to be a drug with very good tolerability over the last few years. In people without diabetes, high doses of up to 800 mg per day have been tested, with good tolerability.

The following adverse effects of empagliflozin are often observed in people with diabetes:

- Urinary tract infections, especially fungal infections. These are usually harmless and can be treated well.
- Diabetes patients with absent or reduced own insulin production are at increased risk for ketoacidosis. Ketoacidosis means that acidic substances accumulate in the blood. In people without diabetes, there are no known cases of ketoacidosis associated with empagliflozin. In people with hypoglycaemia after gastric bypass surgery without diabetes, ketoacidosis is very unlikely.
- The risk of hypoglycaemia is increased if other diabetes medications are taken at the same time (exclusion criterion for study participation), which themselves can lead to hypoglycaemia (especially insulin).

Irrespective of taking the medicine, there are the following other risks:

- Wearing the continuous glucose monitoring device may cause skin irritation.
- The insertion of the indwelling vein cannula for blood sampling at visit 1 and 2 can lead to bruising and very rarely to phlebitis.
- The continuous glucose monitoring device must be removed in case of certain examinations (especially imaging procedures). Please inform your investigator if you are scheduled for an imaging examination during the study period.

For women who can become pregnant

There is very limited experience of the use of empagliflozin in pregnant women. Animal studies have shown no evidence of damage to fertility or development of the offspring in the womb. Due to possible effects on the development of the child in humans, the use of empagliflozin during pregnancy should be avoided. We therefore perform a urine pregnancy test before each treatment phase in women of childbearing age. Women of childbearing age must use a reliable method of contraception (hormonal method such as the pill or IUD) throughout the treatment.
If you nevertheless become pregnant during the study, you must inform your investigator immediately and you may not continue to participate in the study. In this case, you will be asked to provide information about the course and outcome of the pregnancy. The investigator will discuss the further procedure with you.
There is no information on whether empagliflozin passes into breast milk in humans. Data from animal studies have shown that empagliflozin passes into the milk and has adverse effects on the development of the offspring after birth. A risk for the newborn/infant in humans cannot be excluded. Breastfeeding must be interrupted during the study participation - if participation in the study is nevertheless desired.

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7. Alternatives

Participation in the study is associated with opportunities and risks. The options for treating postprandial hypoglycaemia after gastric bypass surgery are limited and there are no approved drugs. Dietary changes (especially avoiding sugar in the diet) can be very effective, but are not always sufficient and often difficult to implement in everyday life. The active ingredient "acarbose" inhibits sugar absorption in the small intestine. Its effectiveness against postprandial hypoglycaemia has been proven in studies. However, acarbose is often not tolerated (flatulence, abdominal cramps) and taking it before every meal is not user-friendly. Acarbose is also no longer available in Switzerland. Other substances are very expensive, can have serious side effects and have only been used in isolated cases so far. Your investigator will inform you about this during the interview.

8. Results

There are

1. Results of the study that directly affect you,
2. Results of the study that arise by chance (so-called random results)
3. Final results of the entire study.

Re 1: Your investigator will inform you about all new results and findings that are important for you personally during the course of the study. You will be informed verbally and in writing and can then decide again whether you would like to continue to participate in the study.

Re 2: Incidental findings are so-called "concomitant results", i.e. results that were not looked for but were found by chance. In the case of our study, these can be findings from blood or urine collections. In the case of incidental findings, you will be informed if these findings are relevant to your health. This means that such findings will be communicated to you if a previously unknown disease has been found by chance or if a disease that has not yet occurred can be prevented through prevention. If you do not want to be informed about this, please talk to your investigator.

Re 3: Your investigator may send you a summary of the overall results at the end of the study.

9. Confidentiality of data and samples

Personal and medical data will be collected as part of the study. Only a few professionals will see your unencrypted data, and only to perform tasks within the study. When data is collected for study purposes, it is encrypted. Encryption means that all data that could be used to recognise you (e.g. name, date of birth) is replaced by a code (key). This means that people who do not know the key cannot draw any conclusions about your identity. Within the Inselspital, the data can be viewed by authorised persons even without encryption. The key list always remains in the hospital. In the event of a manuscript publication, the summarised data cannot be traced back to you as a person. Your name will never appear on the internet or in a publication. Sometimes a journal requires the submission of individual data (so-called raw data) for publication. If personal data has to be submitted, it is always encrypted and no inference can be drawn to you as an individual. All people who have access to your data within the framework of the project are subject to the duty of confidentiality. The data protection regulations are observed and as a participant you have the right to view your data at any time.

Your encrypted data and samples will be stored in a secure study database or biobank at the University Department of Diabetology, Endocrinology, Nutritional Medicine and Metabolism (UDEM) at the Inselspital Bern for at least 10 years. It is possible that your data and samples will be used in the future for new, as yet undefined scientific projects. For this purpose, they may be sent to another database in Switzerland or abroad. The study director must ensure that the destination country guarantees a standard of data protection equivalent to that guaranteed in Switzerland. For this further use, we ask you to sign another consent form at the very end of this document. The project management is responsible for compliance with national and international data protection

regulations and for the proper storage of data and samples. An equivalent level of data protection is guaranteed abroad.
This study may be reviewed by the competent ethics committee, the medicines authority Swissmedic or by the institution conducting the study. For these reviews, the study director may have to disclose your personal and medical data. All persons must maintain absolute confidentiality. We will comply with all data protection regulations and will not disclose your name in any publication or on the internet. There is a possibility that we may contact your GP to obtain information about your medical condition.

10. Resignation
You can withdraw from the study at any time. In this case, however, the data and samples collected up to that point will still be evaluated in encrypted form. In the event of withdrawal, your data and samples will continue to be stored in encrypted form. Please consider whether you agree to this before you take part in the study.

11. Compensation
If you participate in this study, you will receive compensation of CHF 300.
We will reimburse you for expenses such as travel expenses incurred as a result of participation.
No costs will be incurred by you or your health insurance company as a result of participation.

12. Liability
The Inselspital, which is responsible for conducting the study, is liable for any damage that you may suffer in connection with the drug and/or the research activities (e.g. examinations). The requirements and procedure for this are regulated by law. The Inselspital Bern has therefore taken out insurance with Zurich Insurance Company Ltd to cover liability in the event of damage.
Should you suffer any damage as a result of participating in this study, please contact your investigator or the above-mentioned insurance company (Zurich Insurance Company Ltd, Mythenquai 2, 8002 Zurich).

13. Funding
The study is funded by the Swiss National Fund for the Promotion of Scientific Research. The drug is provided by Boehringer Ingelheim.

14. Contact person(s)
You may ask questions about study participation at any time. Also, if you have any uncertainties or emergencies that arise during or after the study, please contact:

Prof. Dr. med. et phil. Lia Bally (principal investigator)
Head of Research, Head of Department Nutrition, Metabolism and Obesity
University Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism
Inselspital, 3010 Bern
lia.bally@insel.ch
031 632 36 77

During the study, you can reach us at any time on the following telephone numbers:
Contact for general questions
Study physician: Antonio Ferreira
Telephone: +41 31 66 4 23 55
E-mail: antonio.ferreira@insel.ch

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24/7 EMERGENCY CONTACT

1. Study physician: Antonio Ferreira
   Telephone: +41 31 66 4 23 55
2. Study physician: Andreas Melmer
   Telephone: +41 78 705 49 53
3. Principal investigator: Lia Bally
   Telephone: +41 31 63 2 36 77

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Informed consent

Written informed consent to participate in a clinical trial

Please read this form carefully. Please ask if there is anything you do not understand or would like to know. Your written consent is required for participation.

BASEC-number (after submission):	2021-01187
Title of the study **(scientific and lay language):**	Randomized, double-blind, placebo-controlled crossover trial assessing the impact of the SGLT2 inhibitor empagliflozin on postprandial hypoglycaemia after gastric bypass (the DEEP-Empa trial) Effect of empagliflozin on hypoglycaemia after gastric bypass surgery a randomised-controlled double-blind study
Responsible institution **(Sponsor with address):**	University Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism Freiburgstrasse 15, 3010 Bern
Place of implementation:	Inselspital
Investigator at the study site: Surname and first name in block capitals:	Prof. Dr. med. et. phil. Lia Bally
Participant: Surname and first name in block capitals: Date of birth:	

- I have been informed verbally and in writing by the undersigned investigator about the purpose, the procedure of the study with possible advantages and disadvantages as well as possible risks.
- I am participating in this study voluntarily and accept the contents of the written information given to me. I have had sufficient time to make my decision.
- My questions in connection with participation in this study have been answered. I will keep the written information and receive a copy of my written informed consent.
- I was informed about possible alternatives to the study, e.g. other treatment procedures.
- I agree that my family doctor will be informed about my participation in the study.
- In the event of further treatment outside the trial centre, I authorise my post-treatment physicians to transmit my data relevant to the study to the investigator.
- I agree that the responsible experts of the sponsor, the responsible ethics committee and the medicines authority Swissmedic may inspect my unencrypted data for testing and control purposes, but in strict compliance with confidentiality.
- I will be informed of any results or incidental findings that directly affect my health. If I do not wish to be informed, I will inform my investigator.
- I can withdraw from the study participation at any time and without giving reasons. My continued medical treatment is guaranteed regardless of study participation. The data and samples collected up to the time of withdrawal will still be evaluated within the framework of the study.

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- I am informed that the Inselspital has taken out an insurance policy covering damage attributable to the research project.
- I am aware that the obligations stated in the information document must be complied with. In the interest of my health, the investigator may exclude me from the study at any time.

Place, date	Signature of the participant

Confirmation of the investigator: I hereby confirm that I have explained the nature, significance and scope of the study to this participant. I assure that I will fulfil all obligations in connection with this study in accordance with the law applicable in Switzerland. If, in the course of the study, I learn of any aspects that could influence the participant's willingness to take part in the study, I will inform him/her immediately.

Place, date	Surname and first name of the investigator in capital letters Signature of the investigator

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Declaration of consent for further use of data and biological material in encrypted form

BASEC-number (after submission):	2021-01187
Title of the study **(scientific and lay language):**	Randomized, double-blind, placebo-controlled crossover trial assessing the impact of the SGLT2 inhibitor empagliflozin on postprandial hypoglycaemia after gastric bypass (the DEEP-Empa trial) Effect of empagliflozin on hypoglycaemia after gastric bypass surgery a randomised-controlled double-blind study
Participant: Surname and first name in block capitals: Date of birth:	

I give permission for my encrypted data and samples from this study to be further used for medical research. The samples will be stored in a biobank at the Inselspital Bern for future, as yet undefined research projects for an indefinite period of time.

I understand that the samples are encrypted and the key is stored securely.
The data and samples can be sent to other data and biobanks in Switzerland and abroad for analysis if they adhere to the same standards as in Switzerland. All legal requirements for data protection are complied with.

I decide voluntarily and can withdraw this decision at any time. If I withdraw, the data and samples will remain encrypted, as anonymization in the present project would only be possible with a disproportionate effort in terms of time, costs and manpower. I only inform my investigator and do not have to justify this decision. After revocation, my data and samples will no longer be made available for enticement for new research projects.

Normally, all data and samples are evaluated as a whole and the results are published in summary form. If there is a result that is important for my health, it is possible that I will be contacted. If I do not wish to be contacted, I will inform my investigator.

If results from the data and samples are commercialised, I have no claim to share in the commercial use.

Place, date	Signature of the participant

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Confirmation of the investigator: I hereby confirm that I have explained to this participant the nature, significance and scope of the further use of samples and/or data.

Place, date	Surname and first name of the investigator in capital letters Signature of the investigator

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Figure 1: Study procedure