BMJ Open

Randomized, double-blind, placebo-controlled crossover trial assessing the impact of the SGLT2 inhibitor empagliflozin on postprandial hypoglycaemia after gastric bypass

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-060668
Article Type:	Protocol
Date Submitted by the Author:	15-Mar-2022
Complete List of Authors:	Ferreira, Antonio; University of Bern, Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism Emara, Ahmed Fahiem Abdelsalam; University of Bern, Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism Herzig, David; University of Bern, Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism Melmer, Andreas; University of Bern, Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism Vogt, Andreas; Inselspital Universitatsspital Bern Nakas, Christos T.; University of Thessaly Facchinetti, Andrea; University of Padua Department of Information Engineering Dalla Man, Chiara; University of Padova, Department of Information Engineering Bally, Lia; University of Bern, Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism
Keywords:	General endocrinology < DIABETES & ENDOCRINOLOGY, General diabetes < DIABETES & ENDOCRINOLOGY, SURGERY

Randomized, double-blind, placebo-controlled crossover trial assessing the impact of the SGLT2 inhibitor empagliflozin on postprandial hypoglycaemia after gastric bypass

DEEP-EMPA TRIAL

Clinical Study Protocol

Antonio Ferreira[1], Ahmed Fahiem Abdelsalam Emara[1], David Herzig[1], Andreas Melmer[1], Andreas Vogt[2], Christos T. Nakas[3], Andrea Facchinetti[4], Chiara Dalla Man[4], Lia Bally[1]

[1]Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism, Inselspital, Bern University Hospital, University of Bern, Switzerland.

[2]Department of Anaesthesiology and Pain Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland.

[3]Laboratory of Biometry, School of Agriculture, University of Thessaly, Nea Ionia Magnesia, Greece.

[4]Department of Information Engineering, University of Padova, Padova, Italy

Corresponding author:

Prof. Dr. med. et. Phil. Lia Bally

Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism

Inselspital, Bern University Hospital, University of Bern, Switzerland

Phone: +41 (0)31 632 31 44

Email: lia.bally@insel.ch

Abstract

Introduction:

Postprandial hypoglycaemia after gastric bypass surgery (also known as postbariatric hypoglycaemia or PBH) is an increasingly encountered clinical problem. PBH is characterized 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 25mg, a SGLT2-inhibitor, to reduce glucose excursions and hypoglycaemia burden in patients with PBH after gastric bypass surgery.

Methods and analysis:

In a prospective, single-centre, randomized, 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 <3.0mmol/L). Eligible patients will be randomized to receive empagliflozin 25mg and placebo once daily, each for 20 days, in random order. Study periods will be separated by a 2-6 week 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 ± standard deviation plus 95 % confidences intervals with p-values and hypothesis testing for primary and secondary outcomes according to intention-to-treat. Secondary outcomes include continuous glucose monitoring (CGM)-based outcomes, further metabolic measures and safety.

Ethics and dissemination:

The DEEP-Empa trial 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.

Trial registration:

This trial is registered with Clinicaltrial.gov (NCT05057819) and the Swiss National Clinical Trials Portal (SNCTP000004622).

Strengths and limitations of this study

- First study that investigates the effect of empagliflozin 25mg on glycaemic variability and hypoglycaemia burden in patients with PBH
- Randomized, 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 25mg in reducing PBH in unrestricted daily living
- Single-site design and short time-frame may limit applicability of findings to different contexts

Keywords:

Postbariatric hypoglycaemia, PBH, Gastric bypass surgery, SGLT2 inhibitor, Empagliflozin

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 recognized 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 among postbariatric patients may be as high as 30% of patients undergoing RYGB [5, 6]. In affected individuals, hypoglycaemic episodes occur 1-3h after meals [7]. PBH events may be accompanied by neuroglycopenic symptoms, but their sensitivity has recently reported to be poor [8]. This is in line with previous results suggesting a high prevalence of asymptomatic PBH patients [4]. 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 hospitalization was 50% [8]. 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 [9]. Additional factors such as diminished insulin clearance, alterations in postprandial bile kinetics, and blunted neuro-endocrine counter-regulation may be further contributors [10-13].

In the absence of approved pharmacotherapies for PBH, dietary modification, mainly carbohydrate restriction is first-line therapy [14]. Second-line approaches include off-label use of acarbose and other systemic acting drugs such as somatostatin analogues, diazoxide and/or

calcium channel blockers. These medications are limited by poor tolerability, inconvenient mode of administration, high costs or restricted availability (e.g. acarbose no longer available on the Swiss market) [7, 15].

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 to placebo (2 vs. 7 translating into a 74% risk reduction) [16]. Empagliflozin is an inhibitor of the sodium-glucose cotransporter 2 (SGLT2) [17]. SGLT2 resides in the brush border membrane of proximal tubular cells in the kidney and reabsorbs ~90 % of glucose filtered at the glomerulus [18]. SGLT2 inhibitors block the physiological glucose reabsorption in the proximal tubule from the glomerular filtrate, thereby reducing postprandial hyperglycaemia through increased urinary glucose excretion. Additionally, glucosuria produced by SGLT2 inhibition stimulates endogenous glucose production, which is accompanied by an increase in plasma glucagon levels [19-21]. Empagliflozin 10 mg or 25 mg once daily is approved for the treatment of type 2 diabetes. In healthy, non-diabetic, normoglycaemic volunteers, a dose of 25 mg once daily was more effective in inducing glucosuria than 10 mg. In addition to improved glucose control, empagliflozin was shown to decrease cardiovascular mortality, death from any cause, hospitalizations for heart failure, decline kidney function and need for renal replacement therapy in patients with type 2 diabetes [22-24].

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 [17]. No cases of euglycaemic ketoacidosis in individuals without diabetes treated with SGLT2 inhibitors have been reported.

Taken together, the pharmacodynamics profile of empagliflozin and the preliminary data in the target population suggest that SGLT2 inhibitors could effectively reduce glycaemic variability and hypoglycaemia burden in PBH patients whilst 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 has therapeutic potential to lower the burden of PBH.

Primary objective

To assess the efficacy of empagliflozin to reduce glucose excursions in individuals with PBH.

Secondary objectives

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

Further objectives

To determine the impact of empagliflozin on glucose-insulin homeostasis.

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

To assess the effect of empagliflozin on ketone levels.

To assess carbohydrate-based meal patterning whilst taking empagliflozin.

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.

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
- Peak plasma glucose during the mixed-meal test
- Percent time spent with sensor glucose >10.0mmol/L

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

- Mean coefficient of variability based on sensor glucose

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

- Proportion of participants experiencing hypoglycaemia (defined as plasma glucose<3.0mmol/L) during the mixed meal tolerance test.
- Nadir plasma glucose during the mixed-meal test
- Percent time spent with sensor glucose <3.0mmol/L
- Percent time spent with sensor glucose <2.8mmol/L
- Frequency of postprandial symptoms based on a modified Edinburgh Hypoglycaemia Symptom Scale

Exploratory outcomes

- Insulin response during the mixed-meal test (incremental AUC from 0 to 120min following meal ingestion)
- Measures of beta-cell function, insulin sensitivity and first-pass hepatic insulin extraction using the oral minimal model method calculated using data from the mixed-meal test
- Total amount of daily excreted glucose (g/24h) measured in the 24h urine collection
- Glucagon response during the mixed-meal test (incremental AUC from 0 to 120min following meal ingestion)
- Ketone levels (3-beta-hydroxybutyrate) during the mixed-meal test
- Average daily meal frequency (carbohydrate content ≥30g/24h and <30g/24h) assessed during the treatment periods

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 standardized 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 4th 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 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 randomized, double-blind, placebo-controlled, crossover, single-centre study. Twenty-two participants will be randomized in equal proportions into two groups (11 participants per group). In one group, 25 mg once daily empagliflozin, the investigational medicinal product (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 2x20 days with a randomized crossover allocation and an interspersed wash-out period of 2-6 weeks (Figure 1).

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 <3.0mmol/L within the last three months before recruitment. This threshold has been recognized by the International Hypoglycaemia Study Group as clinically important hypoglycaemia due its association with neuroglycopenic symptoms and adverse health effects [25]. Based on findings of a recent study, the threshold of 3.0mmol/L irrespective of the presence of neuroglycopenic symptoms was proposed to signify clinically important hypoglycaemia specifically in the PBH population [8]. Recruitment occurs via local advertisements and referrals from internal and external bariatric physicians. Written

informed consent will be obtained before any study-related procedures. Study participation will be reimbursed for their efforts and time (CHF 300 plus study-related travel costs).

Exclusion criteria:

I. Diabetes on anti-diabetic treatment (insulin and/or non-insulin agents);
II. Chronic kidney disease (defined as CKD-EPI eGFR < 60 mL/min per 1.73 m2 body surface area);
III. Genito-urinary infection, if not treated successfully;
IV. Pregnant and lactating women (urine pregnancy test to be performed for women of childbearing potential [defined as women who are not surgically sterilized/ hysterectomized, 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 IUD]);
V. Inability to understand and follow the protocol;
VI. Known allergy to the study drug;
VII. Participation in another interventional clinical trial overlapping with the current trial

Randomization

The randomization to the treatment sequence will be performed by the principle of simple randomization using a computer-generated sequence. The randomization 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 randomized 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 randomization, participants will attend a baseline visit (see Figure 1). Participants will remain on the assigned IMP/placebo for 20 days. During the last day of treatment, participants will perform a 24h urine collection and the following day attend the clinical research facility for a mixed meal tolerance test. Frequent blood sampling for plasma glucose, insulin, C-peptide and glucagon at baseline and 10 min, 20 min, 30 min, 60 min, 90 min, 120 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. The standardised meal will consist of a typical solid breakfast (545kcal, 73g of carbohydrates, 22g of fat and 12g of protein). 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, e.g. ≥30 vs. <30g) 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 -1.46mmol/L (SD 0.31mmol/L). With a sample size of 17 participants, the study would detect a mean paired-difference of 0.3mmol/L (this corresponds to an effect size of 0.75 with the assumption of a within participant

SD of 0.35mmol/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 3.1.9.6.

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 to 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 (e.g. additional validations, generation of new variables), definitions (e.g. analysis sets), and statistical analyses (e.g. models, outputs such as tables and graphs). Results from statistical analyses will be presented as effect measures plus 95 % confidences intervals. 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 (ITT) basis, whereby all randomized participants will be analysed in the allocated group regardless of any protocol violations such as cross-overs (which can only happen accidently 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 (PP) 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 (i.e. to be compliant, patients must take at least 16 tablets); or 3) missed intake on 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 (e.g. 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 for the following reasons: 1) the long wash out period accounts for this by design and 2) such gate-keeping tests lead to inflated type I errors.

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 % confidences intervals. 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 CRFs are implemented electronically using the study database REDCap®. REDCap® supports data analysis by integrated tools for creating reports and charts [26, 27]. 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.

Abbreviations

PBH : postbariatric hypoglycaemia; mg: milligram; SD: standard deviation; CGM: continuous glucose monitoring; RYGB: Roux-en-Y gastric bypass; SGLT2: sodium-glucose cotransporter 2; MAGE: Mean amplitude of glucose excursion; AUC: Area under the curve; IMP: investigational medicinal product; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; eGFR : estimated glomerular filtration rate; IUD: Intrauterine contraceptive device; SO: Scientific Officer; ITT: intention-to-treat; PP: per-protocol; SAEs: Serious Adverse Events; AESIs: Adverse Events of Special Interest; CRF: Case Report Form; REDCap: Research Electronic Data Capture; CSV: Comma-separated values; ICH: International Council for Harmonisation; Q1: first quarter; SNF: Schweizerischer Nationalfonds; SNSF: Swiss national science foundation;

Declarations

Ethics and dissemination

The DEEP-Empa trial will be performed in accordance with the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice issues by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), the Swiss Law and Swiss regulatory authorities' requirements. The Ethics Committee Bern and Swissmedic will receive annual reports and will be notified of safety events or measures, as well as protocol amendments or change in study status (start/stop). The study was approved by the Ethics Committee Bern in September 2021, and by Swissmedic in November 2021. Registration was issued at ClinicialTrials.gov (NCT05057819). Patient recruitment started in December 2021 and at the time of submission, five participants have been enrolled. Study completion is anticipated in December 2022, and

first results are expected in Q1 of 2023. No publications containing results of this study have already been published or submitted to any journal.

Consent for publication

Not applicable.

Availability of data and materials

Datasets generated during the study will be made available upon request.

Competing interests

Authors declare no competing interests. Boehringer Ingelheim provides the IMP. Boehringer Ingelheim will have the right to comment on any manuscript derived from this study but will not be allowed to interfere in the process of publishing results in any form deemed appropriate by the investigators.

Funding

The study is fully supported by the Swiss National Science Foundation (PCEGP3_186978/1). The trial will also reive intramural support of the Bern University Hospital for local laboratory analyses.

Author's contributions

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. LB, DH and CTN wrote the statistical analysis plan. LB, DH and AF coordinate the study. LB and AF are involved

in the recruitment of patients and patient care. LB, AF, AE drafted the first protocol manuscript.

All authors contributed to the manuscript and all authors read and approved the final version.

Email addresses of authors:

Lia Bally lia.bally@insel.ch

Antonio Ferreira antonio.ferreira@insel.ch

David Herzig david.herzig@extern.insel.ch

Ahmed Fahiem Abdelsalam Emara ahmed.emara@insel.ch

Andreas Melmer andreas.melmer@insel.ch

Andreas Vogt andreas.vogt@insel.ch

Chiara Dalla Man chiara.dallaman@unipd.it

Andrea Facchinetti andrea.facchinetti@dei.unipd.it

Christos T.Nakas cnakas@gmail.com; christos.nakas@extern.insel.ch

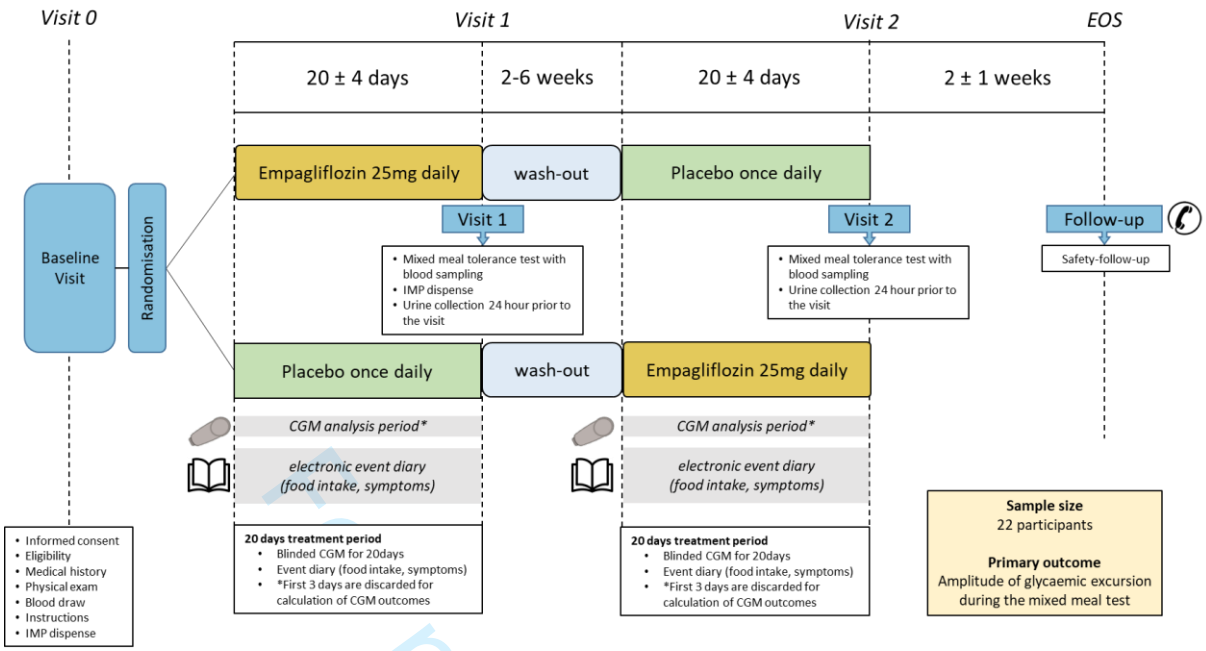
References

1. Hofsø, D., et al., *Gastric bypass versus sleeve gastrectomy in patients with type 2 diabetes (Oseberg): a single-centre, triple-blind, randomised controlled trial.* Lancet Diabetes Endocrinol, 2019. **7**(12): p. 912-924.
2. Angrisani, L., et al., *Bariatric Surgery and Endoluminal Procedures: IFSO Worldwide Survey 2014.* Obes Surg, 2017. **27**(9): p. 2279-2289.
3. Lee, C.J., et al., *Risk of post-gastric bypass surgery hypoglycemia in nondiabetic individuals: A single center experience.* Obesity (Silver Spring), 2016. **24**(6): p. 1342-8.
4. Halperin, F., et al., *Continuous glucose monitoring for evaluation of glycemic excursions after gastric bypass.* J Obes, 2011. **2011**: p. 869536.
5. Capristo, E., et al., *Incidence of Hypoglycemia After Gastric Bypass vs Sleeve Gastrectomy: A Randomized Trial.* J Clin Endocrinol Metab, 2018. **103**(6): p. 2136-2146.
6. Lazar, L.O., et al., *SYMPTOMATIC AND ASYMPTOMATIC HYPOGLYCEMIA POST THREE DIFFERENT BARIATRIC PROCEDURES: A COMMON AND SEVERE COMPLICATION.* Endocr Pract, 2019.
7. Salehi, M., et al., *Hypoglycemia After Gastric Bypass Surgery: Current Concepts and Controversies.* J Clin Endocrinol Metab, 2018. **103**(8): p. 2815-2826.

8. Craig, C.M. and T.L. McLaughlin, *Defining clinically important hypoglycemia in patients with postbariatric hypoglycemia.* Surg Obes Relat Dis, 2021. **17**(11): p. 1865-1872.
9. Salehi, M., A. Gastaldelli, and D.A. D'Alessio, *Blockade of glucagon-like peptide 1 receptor corrects postprandial hypoglycemia after gastric bypass.* Gastroenterology, 2014. **146**(3): p. 669-680.e2.
10. Salehi, M., A. Gastaldelli, and D.A. D'Alessio, *Altered islet function and insulin clearance cause hyperinsulinemia in gastric bypass patients with symptoms of postprandial hypoglycemia.* J Clin Endocrinol Metab, 2014. **99**(6): p. 2008-17.
11. Mulla, C.M., et al., *Plasma FGF-19 Levels are Increased in Patients with Post-Bariatric Hypoglycemia.* Obes Surg, 2019. **29**(7): p. 2092-2099.
12. Abrahamsson, N., et al., *Gastric Bypass Reduces Symptoms and Hormonal Responses in Hypoglycemia.* Diabetes, 2016. **65**(9): p. 2667-75.
13. van den Broek, M., et al., *Altered bile acid kinetics contribute to postprandial hypoglycaemia after Roux-en-Y gastric bypass surgery.* Int J Obes (Lond), 2021. **45**(3): p. 619-630.
14. Suhl, E., et al., *Medical nutrition therapy for post-bariatric hypoglycemia: practical insights.* Surg Obes Relat Dis, 2017. **13**(5): p. 888-896.
15. Valderas, J.P., et al., *Acarbose improves hypoglycaemia following gastric bypass surgery without increasing glucagon-like peptide 1 levels.* Obes Surg, 2012. **22**(4): p. 582-6.
16. Hepprich, M., et al., *Postprandial Hypoglycemia in Patients after Gastric Bypass Surgery Is Mediated by Glucose-Induced IL-1β.* Cell Metab, 2020. **31**(4): p. 699-709.e5.
17. Tahrani, A.A., A.H. Barnett, and C.J. Bailey, *SGLT inhibitors in management of diabetes.* Lancet Diabetes Endocrinol, 2013. **1**(2): p. 140-51.
18. Kanai, Y., et al., *The human kidney low affinity Na+/glucose cotransporter SGLT2. Delineation of the major renal reabsorptive mechanism for D-glucose.* J Clin Invest, 1994. **93**(1): p. 397-404.
19. Merovci, A., et al., *Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production.* J Clin Invest, 2014. **124**(2): p. 509-14.
20. DeFronzo, R.A., L. Norton, and M. Abdul-Ghani, *Renal, metabolic and cardiovascular considerations of SGLT2 inhibition.* Nat Rev Nephrol, 2017. **13**(1): p. 11-26.
21. Ferrannini, E., et al., *Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients.* J Clin Invest, 2014. **124**(2): p. 499-508.
22. Zinman, B., et al., *Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes.* N Engl J Med, 2015. **373**(22): p. 2117-28.
23. Wanner, C., S.E. Inzucchi, and B. Zinman, *Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes.* N Engl J Med, 2016. **375**(18): p. 1801-2.
24. Seman, L., et al., *Empagliflozin (BI 10773), a Potent and Selective SGLT2 Inhibitor, Induces Dose-Dependent Glucosuria in Healthy Subjects.* Clin Pharmacol Drug Dev, 2013. **2**(2): p. 152-61.
25. *Glucose Concentrations of Less Than 3.0 mmol/L (54 mg/dL) Should Be Reported in Clinical Trials: A Joint Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes.* Diabetes Care, 2017. **40**(1): p. 155-157.
26. Harris, P.A., et al., *The REDCap consortium: Building an international community of software platform partners.* J Biomed Inform, 2019. **95**: p. 103208.
27. Harris, P.A., et al., *Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support.* J Biomed Inform, 2009. **42**(2): p. 377-81.

Figures

Figure 1. The Deep Empa Trial study design. CGM, continuous glucose monitoring; IMP, investigational medicinal product; EOS, end of study visit.



Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	Protocol V1 29.12.2021
Funding	#4	Sources and types of financial, material, and other support	Page 17

Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	Page 17
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	Page 1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Page 17
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Page 17
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 4-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	Page 4-6
Objectives	#7	Specific objectives or hypotheses	Page 6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	Page 9
Methods: Participants,			

interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 9-12
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 10
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 9
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	Page 9-12
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	Page 9-12
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 9-12
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 7-8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Page 9

Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 12
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 10
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 12
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Page 9-12
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 17
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 11
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Page 11
Methods: Data collection, management, and analysis			

Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 11-15
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 9-12
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 12-15
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 12-15
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 12-15
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 12-15
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the	N/A

		protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Page 12-15
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page 12-15
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 12-15
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	Page 16/17
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 16/17
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 15
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 16/17

Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 16/17
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page 16/17
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Available upon request
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-060668.R1
Article Type:	Protocol
Date Submitted by the Author:	21-Jun-2022
Complete List of Authors:	Ferreira, Antonio; University of Bern, Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism Emara, Ahmed Fahiem Abdelsalam; University of Bern, Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism Herzig, David; University of Bern, Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism Melmer, Andreas; University of Bern, Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism Vogt, Andreas; Inselspital Universitatsspital Bern Nakas, Christos T.; University of Thessaly Facchinetti, Andrea; University of Padua Department of Information Engineering Dalla Man, Chiara; University of Padova, Department of Information Engineering Bally, Lia; University of Bern, Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Nutrition and metabolism, Surgery, Pharmacology and therapeutics
Keywords:	General endocrinology < DIABETES & ENDOCRINOLOGY, General diabetes < DIABETES & ENDOCRINOLOGY, SURGERY

Study protocol for a 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

Antonio Ferreira[1], Ahmed Fahiem Abdelsalam Emara[1], David Herzig[1], Andreas Melmer[1], Andreas Vogt[2], Christos T. Nakas[3], Andrea Facchinetti[4], Chiara Dalla Man[4], Lia Bally[1]

[1]Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism, Inselspital, Bern University Hospital, University of Bern, Switzerland.

[2]Department of Anaesthesiology and Pain Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland.

[3]Laboratory of Biometry, School of Agriculture, University of Thessaly, Nea Ionia Magnesia, Greece.

[4]Department of Information Engineering, University of Padova, Padova, Italy

Corresponding author:

Prof. Dr. med. et. Phil. Lia Bally

Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism

Inselspital, Bern University Hospital, University of Bern, Switzerland

Phone: +41 (0)31 632 31 44

Email: lia.bally@insel.ch

Abstract

Introduction:

Postprandial hypoglycaemia after gastric bypass surgery (also known as postbariatric hypoglycaemia or PBH) is an increasingly encountered clinical problem. Postbariatric hypoglycaemia is characterized 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 25mg, a SGLT2-inhibitor, to reduce glucose excursions and hypoglycaemia burden in patients with postbariatric hypoglycaemia after gastric bypass surgery.

Methods and analysis:

In a prospective, single-centre, randomized, double-blind, placebo-controlled, crossover trial, we plan to enrol 22 adults (≥18 years) with postbariatric hypoglycaemia after Roux-en-Y gastric bypass surgery (plasma or sensor glucose <3.0mmol/L). Eligible patients will be randomized to receive empagliflozin 25mg and placebo once daily, each for 20 days, in random order. Study periods will be separated by a 2-6 week 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 ± standard deviation plus 95 % confidences intervals with p-values and hypothesis testing for primary and secondary outcomes according to intention-to-treat. Secondary outcomes include continuous glucose monitoring (CGM)-based outcomes, further metabolic measures and safety.

Ethics and dissemination:

The DEEP-Empa trial 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.

Trial registration:

This trial is registered with Clinicaltrial.gov (NCT05057819) and the Swiss National Clinical Trials Portal (SNCTP000004622).

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
- Randomized, 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 25mg in reducing postbariatric hypoglycaemia in unrestricted daily living
- Single-site design and short time-frame may limit applicability of findings to different contexts

Keywords:

Postbariatric hypoglycaemia, PBH, Gastric bypass surgery, SGLT2 inhibitor, Empagliflozin

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 recognized 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 postbariatric hypoglycaemia may be as high as 30% of patients undergoing Roux-en-Y gastric bypass [5, 6]. The complication is also observed in patients with type 2 diabetes before surgery, independently of its remission [7]. Postbariatric hypoglycaemia manifests 1-3h 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 postbariatric hypoglycaemia-induced loss of consciousness or hospitalization 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 postbariatric hypoglycaemia, 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 (e.g. 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 postbariatric hypoglycaemia and significantly lowered the proportion of patients experiencing hypoglycaemia during a standardised mixed meal tolerance test compared to 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 postbariatric hypoglycaemia patients suggest that SGLT2 inhibitors could effectively reduce glycaemic variability and hypoglycaemia burden in this population whilst showing high tolerability and convenience of administration.

The DEEP-EMPA in randomised double-blind crossover trial shall address this question by contrasting the efficacy of empagliflozin 25mg versus placeco on glucose excursions and hypoglycaemia burden in patients with postbariatric hypoglycaemia after RYGB.

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 postbariatric hypoglycaemia.

Primary objective

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

Secondary objectives

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

Further objectives

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

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 whilst 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 mean amplitude of glucose excursion (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 to day 20 of intake of IMP/placebo (i.e. 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 >10.0mmol/L
    - The outcome will be calculated from day 1 to day 20 of intake of IMP/placebo (i.e. 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 to day 20 of intake of IMP/placebo (i.e. 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<3.0mmol/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 <3.0mmol/L
    - The outcome will be calculated from day 1 to day 20 of intake of IMP/placebo (i.e. 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 <2.8mmol/L (in accordance with a recently published International consensus on the diagnosis of postbariatric hypoglycaemia) [28].
    - The outcome will be calculated from day 1 to day 20 of intake of IMP/placebo

(i.e. 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 to day 20 of intake of IMP/placebo.

Exploratory outcomes

- Insulin response during the mixed meal test (incremental AUC from 0 to 120min 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/24h) measured in the 24h 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 120min 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 ≥30g/24h and <30g/24h) 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 standardized 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 4th 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 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 randomized, double-blind, placebo-controlled, crossover, single-centre study. Twenty-two participants will be randomized in equal proportions into two groups (11 participants per group). In one group, 25 mg once daily empagliflozin, the investigational medicinal product (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 2x20 days with a randomized 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 postbariatric hypoglycaemia 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 25mg 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 Roux-en-Y gastric bypass ≥ 1 year ago, and with biochemically confirmed postprandial hypoglycaemia defined as plasma or sensor glucose measurement of <3.0mmol/L within the last three months before recruitment. This threshold has been recognized by the International Hypoglycaemia Study Group as clinically important hypoglycaemia due its association with neuroglycopenic symptoms and adverse health effects [31]. Based on findings of a recent study, the threshold of 3.0mmol/L irrespective of the presence of neuroglycopenic symptoms was proposed to signify clinically important hypoglycaemia specifically in the postbariatric hypoglycaemia 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 supplemental appendix). Study

participation will be reimbursed for their efforts and time (CHF 300 plus study-related travel costs).

Exclusion criteria:

I. Diabetes on anti-diabetic treatment (insulin and/or non-insulin agents);
II. Chronic kidney disease (defined as CKD-EPI eGFR < 60 mL/min per 1.73 m2 body surface area);
III. Genito-urinary infection, if not treated successfully;
IV. Pregnant and lactating women (urine pregnancy test to be performed for women of childbearing potential [defined as women who are not surgically sterilized/ hysterectomized, 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 IUD]);
V. Inability to understand and follow the protocol;
VI. Known allergy to the study drug;
VII. Participation in another interventional clinical trial overlapping with the current trial

Randomization

The randomization to the treatment sequence will be performed by the principle of simple randomization using a computer-generated sequence. The randomization 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 randomized 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 randomization, participants will attend a baseline visit (see Figure 1). Participants will remain on the assigned IMP/placebo for 20 ± 4 days. During day 19 of the IMP intake period, participants will perform a 24h 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 yogurt (500kcal, 74g of carbohydrates, 18g of fat and 12g of protein). Participants will be asked to ingest the meal within 15 minutes 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, 135min, 150min 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 utilization 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, e.g. ≥30 vs. <30g, according to nutritional guidelines for the management of postbariatric hypoglycaemia [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 postbariatric hypoglycaemia, the mean paired-difference (empagliflozin - placebo) of the decrease in plasma glucose following a mixed meal test was -1.46mmol/L (SD 0.31mmol/L). With a sample size of 17 participants, the study would detect a mean paired-difference of 0.3mmol/L (this corresponds to an effect size of 0.75 with the assumption of a within participant SD of 0.35mmol/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 3.1.9.6.

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 to 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 (e.g. additional validations, generation of new variables), definitions (e.g. analysis sets), and statistical analyses (e.g. models, outputs such as tables and graphs). Results from statistical analyses will be presented as effect measures plus 95 % confidences intervals. 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 (ITT) basis, whereby all randomized participants will be analysed in the allocated group regardless of any protocol violations such as cross-overs (which can only happen accidently 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 (PP) 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 (i.e. to be compliant, patients must take at least 16 tablets); or 3) missed intake on 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 (e.g. 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 % confidences intervals. 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 CRFs 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.

Abbreviations

mg: milligram; SD: standard deviation; CGM: continuous glucose monitoring; RYGB: Roux-en-Y gastric bypass; SGLT2: sodium-glucose cotransporter 2; MAGE: Mean amplitude of glucose excursion; AUC: Area under the curve; IMP: investigational medicinal product; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; eGFR : estimated glomerular filtration rate; IUD: Intrauterine contraceptive device; SO: Scientific Officer; ITT: intention-to-treat; PP: per-protocol; SAEs: Serious Adverse Events; AESIs: Adverse Events of Special Interest; CRF: Case Report Form; REDCap: Research Electronic Data Capture; CSV: Comma-separated values; ICH: International Council for Harmonisation; Q1: first quarter; SNSF: Swiss national science foundation;

Declarations

Ethics and dissemination

The DEEP-Empa trial will be performed in accordance with the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical

Practice issues by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), the Swiss Law and Swiss regulatory authorities' requirements. The Ethics Committee Bern and Swissmedic will receive annual reports and will be notified of safety events or measures, as well as protocol amendments or change in study status (start/stop). The study was approved by the Ethics Committee Bern in September 2021, and by Swissmedic in November 2021. Registration was issued at ClinicialTrials.gov (NCT05057819). Patient recruitment started in December 2021 and at the time of submission, five participants have been enrolled. Study completion is anticipated in December 2022, and first results are expected in Q1 of 2023. No publications containing results of this study have already been published or submitted to any journal.

Consent for publication

Not applicable.

Availability of data and materials

Datasets generated during the study will be made available upon request.

Competing interests

Authors declare no competing interests. Boehringer Ingelheim provides the IMP. Boehringer Ingelheim has no role in the design, conductance or interpretation of the trial. Boehringer Ingelheim will have the right to comment on any manuscript derived from this study but will not be allowed to interfere in the process of publishing results in any form deemed appropriate by the investigators.

Funding

The study is fully supported by the Swiss National Science Foundation (PCEGP3_186978/1). The trial will also reive intramural support of the Bern University Hospital for local laboratory analyses.

Author's contributions

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. AFacc. 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 AF coordinate the study. LB and AF are involved in the recruitment of patients and patient care. AV is involved in patient care. LB, AF, AE drafted the first protocol manuscript. All authors contributed to the manuscript and all authors read and approved the final version.

Email addresses of authors:

Lia Bally lia.bally@insel.ch

Antonio Ferreira antonio.ferreira@insel.ch

David Herzig david.herzig@extern.insel.ch

Ahmed Fahiem Abdelsalam Emara ahmed.emara@insel.ch

Andreas Melmer andreas.melmer@insel.ch

Andreas Vogt andreas.vogt@insel.ch

Chiara Dalla Man chiara.dallaman@unipd.it

Andrea Facchinetti andrea.facchinetti@dei.unipd.it

Christos T.Nakas cnakas@gmail.com; christos.nakas@extern.insel.ch

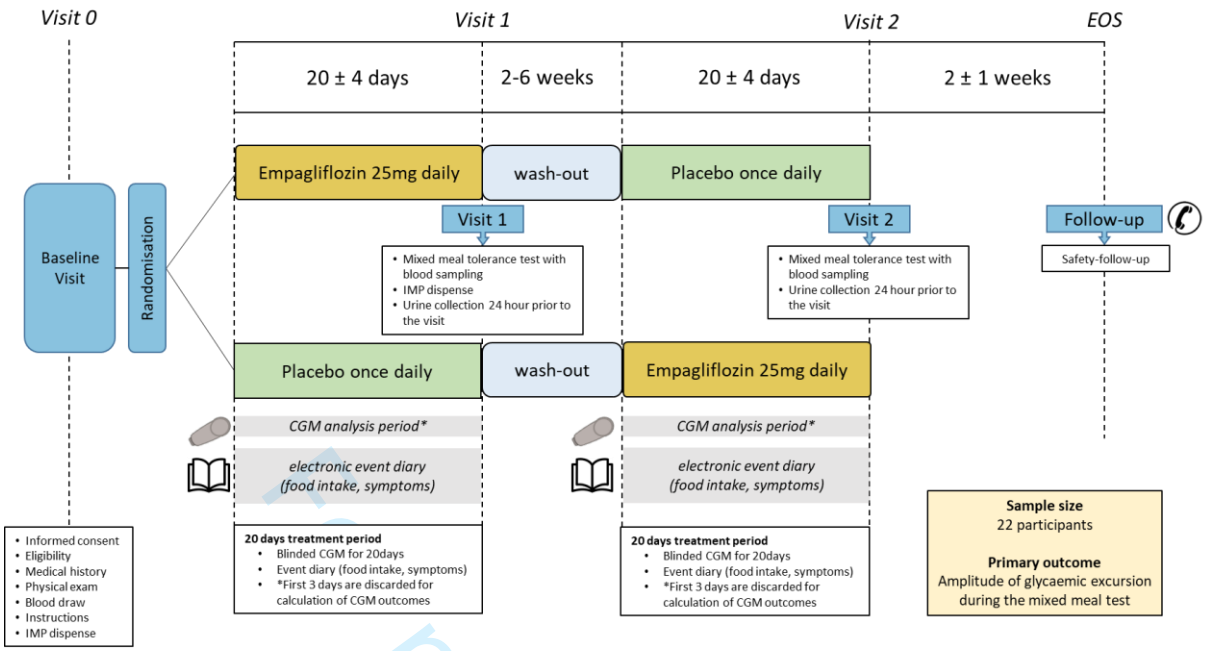
References

1. Hofsø, D., et al., *Gastric bypass versus sleeve gastrectomy in patients with type 2 diabetes (Oseberg): a single-centre, triple-blind, randomised controlled trial.* Lancet Diabetes Endocrinol, 2019. **7**(12): p. 912-924.
2. Angrisani, L., et al., *Bariatric Surgery and Endoluminal Procedures: IFSO Worldwide Survey 2014.* Obes Surg, 2017. **27**(9): p. 2279-2289.
3. Lee, C.J., et al., *Risk of post-gastric bypass surgery hypoglycemia in nondiabetic individuals: A single center experience.* Obesity (Silver Spring), 2016. **24**(6): p. 1342-8.
4. Halperin, F., et al., *Continuous glucose monitoring for evaluation of glycemic excursions after gastric bypass.* J Obes, 2011. **2011**: p. 869536.
5. Capristo, E., et al., *Incidence of Hypoglycemia After Gastric Bypass vs Sleeve Gastrectomy: A Randomized Trial.* J Clin Endocrinol Metab, 2018. **103**(6): p. 2136-2146.
6. Lazar, L.O., et al., *SYMPTOMATIC AND ASYMPTOMATIC HYPOGLYCEMIA POST THREE DIFFERENT BARIATRIC PROCEDURES: A COMMON AND SEVERE COMPLICATION.* Endocr Pract, 2019.
7. Guarino, D., et al., *Postprandial hypoglycaemia after Roux-en-Y gastric bypass in individuals with type 2 diabetes.* Diabetologia, 2019. **62**(1): p. 178-186.
8. Salehi, M., et al., *Hypoglycemia After Gastric Bypass Surgery: Current Concepts and Controversies.* J Clin Endocrinol Metab, 2018. **103**(8): p. 2815-2826.
9. Craig, C.M. and T.L. McLaughlin, *Defining clinically important hypoglycemia in patients with postbariatric hypoglycemia.* Surg Obes Relat Dis, 2021. **17**(11): p. 1865-1872.
10. Salehi, M., A. Gastaldelli, and D.A. D'Alessio, *Blockade of glucagon-like peptide 1 receptor corrects postprandial hypoglycemia after gastric bypass.* Gastroenterology, 2014. **146**(3): p. 669-680.e2.
11. Salehi, M., A. Gastaldelli, and D.A. D'Alessio, *Altered islet function and insulin clearance cause hyperinsulinemia in gastric bypass patients with symptoms of postprandial hypoglycemia.* J Clin Endocrinol Metab, 2014. **99**(6): p. 2008-17.
12. Mulla, C.M., et al., *Plasma FGF-19 Levels are Increased in Patients with Post-Bariatric Hypoglycemia.* Obes Surg, 2019. **29**(7): p. 2092-2099.
13. Abrahamsson, N., et al., *Gastric Bypass Reduces Symptoms and Hormonal Responses in Hypoglycemia.* Diabetes, 2016. **65**(9): p. 2667-75.
14. van den Broek, M., et al., *Altered bile acid kinetics contribute to postprandial hypoglycaemia after Roux-en-Y gastric bypass surgery.* Int J Obes (Lond), 2021. **45**(3): p. 619-630.
15. Suhl, E., et al., *Medical nutrition therapy for post-bariatric hypoglycemia: practical insights.* Surg Obes Relat Dis, 2017. **13**(5): p. 888-896.
16. Valderas, J.P., et al., *Acarbose improves hypoglycaemia following gastric bypass surgery without increasing glucagon-like peptide 1 levels.* Obes Surg, 2012. **22**(4): p. 582-6.
17. Hepprich, M., et al., *Postprandial Hypoglycemia in Patients after Gastric Bypass Surgery Is Mediated by Glucose-Induced IL-1β.* Cell Metab, 2020. **31**(4): p. 699-709.e5.
18. Tahrani, A.A., A.H. Barnett, and C.J. Bailey, *SGLT inhibitors in management of diabetes.* Lancet Diabetes Endocrinol, 2013. **1**(2): p. 140-51.
19. Kanai, Y., et al., *The human kidney low affinity Na+/glucose cotransporter SGLT2. Delineation of the major renal reabsorptive mechanism for D-glucose.* J Clin Invest, 1994. **93**(1): p. 397-404.

20. Seman, L., et al., *Empagliflozin (BI 10773), a Potent and Selective SGLT2 Inhibitor, Induces Dose-Dependent Glucosuria in Healthy Subjects.* Clin Pharmacol Drug Dev, 2013. **2**(2): p. 152-61.
21. Ferrannini, E., et al., *A Phase IIb, randomized, placebo-controlled study of the SGLT2 inhibitor empagliflozin in patients with type 2 diabetes.* Diabetes Obes Metab, 2013. **15**(8): p. 721-8.
22. Merovci, A., et al., *Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production.* J Clin Invest, 2014. **124**(2): p. 509-14.
23. DeFronzo, R.A., L. Norton, and M. Abdul-Ghani, *Renal, metabolic and cardiovascular considerations of SGLT2 inhibition.* Nat Rev Nephrol, 2017. **13**(1): p. 11-26.
24. Ferrannini, E., et al., *Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients.* J Clin Invest, 2014. **124**(2): p. 499-508.
25. Zinman, B., et al., *Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes.* N Engl J Med, 2015. **373**(22): p. 2117-28.
26. Wanner, C., S.E. Inzucchi, and B. Zinman, *Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes.* N Engl J Med, 2016. **375**(18): p. 1801-2.
27. Fernandes, N.J., et al., *Open-Source Algorithm to Calculate Mean Amplitude of Glycemic Excursions Using Short and Long Moving Averages.* Journal of Diabetes Science and Technology, 2021. **16**(2): p. 576-577.
28. Scarpellini, E., et al., *International consensus on the diagnosis and management of dumping syndrome.* Nat Rev Endocrinol, 2020. **16**(8): p. 448-466.
29. Schiavon, M., et al., *Model-Based Assessment of C-Peptide Secretion and Kinetics in Post Gastric Bypass Individuals Experiencing Postprandial Hyperinsulinemic Hypoglycemia.* Frontiers in Endocrinology, 2021. **12**.
30. Cobelli, C., et al., *The oral minimal model method.* Diabetes, 2014. **63**(4): p. 1203-13.
31. *Glucose Concentrations of Less Than 3.0 mmol/L (54 mg/dL) Should Be Reported in Clinical Trials: A Joint Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes.* Diabetes Care, 2017. **40**(1): p. 155-157.
32. Ferrannini, E., et al., *Shift to Fatty Substrate Utilization in Response to Sodium-Glucose Cotransporter 2 Inhibition in Subjects Without Diabetes and Patients With Type 2 Diabetes.* Diabetes, 2016. **65**(5): p. 1190-5.
33. Harris, P.A., et al., *The REDCap consortium: Building an international community of software platform partners.* J Biomed Inform, 2019. **95**: p. 103208.
34. Harris, P.A., et al., *Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support.* J Biomed Inform, 2009. **42**(2): p. 377-81.

Figures

Figure 1. The Deep Empa Trial study design. CGM, continuous glucose monitoring; IMP, investigational medicinal product; EOS, end of study visit.



INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HÔPITAL UNIVERSITAIRE DE BERNE
Universitätsklinik für Diabetologie, Endokrinologie, Ernährungsmedizin und Metabolismus

Anfrage zur Teilnahme an medizinischer Forschung:

Wirkung von Empagliflozin auf Unterzuckerungen nach Magenbypass-Operation – eine randomisiert-kontrollierte Doppelblind-Studie

---

Sehr geehrte Dame, sehr geehrter Herr

Wir fragen Sie hiermit an, ob Sie bereit wären, an unserem Forschungsvorhaben teilzunehmen.

Ihre Teilnahme ist freiwillig. Alle Daten, die in diesem Projekt erhoben werden, unterliegen strengen Datenschutzvorschriften. Das Forschungsvorhaben wird von der *Universitätsklinik für Diabetologie, Endokrinologie, Ernährungsmedizin und Metabolismus* am Inselspital Bern durchgeführt. Bei Interesse informieren wir Sie gerne über die aus dem Projekt gewonnen Erkenntnissen.

In einem Gespräch erklären wir Ihnen die wichtigsten Punkte und beantworten Ihre Fragen. Damit Sie sich bereits jetzt ein Bild machen können, hier das Wichtigste vorweg. Im Anschluss folgen dann weitere, detaillierte Informationen.

Warum führen wir dieses Forschungsprojekt durch?

- Wiederkehrende Unterzuckerungen nach dem Essen können als unerwünschte Spätfolge gewichtsreduzierender Operationen, v.a. einer Magenbypass-Operation, auftreten.
- Zurzeit gibt es kein zugelassenes Medikament zur Behandlung dieser unterwünschten Spätfolge.
- Ein früher eingesetztes Medikament ist in der Schweiz nicht mehr erhältlich und wurde aufgrund von Nebenwirkungen oft nicht vertragen.
- Erste Forschungsergebnisse zeigen, dass der Wirkstoff Empagliflozin, der normalerweise bei Zuckerkrankheit (Diabetes) eingesetzt wird, die Beschwerden von Unterzuckerungen nach Magenbypass-Operation reduzieren können.
- In unserem Forschungsprojekt untersuchen wir die Wirksamkeit von Empagliflozin gegen Unterzuckerungen nach Magenbypass-Operation während 20 Tagen.

Was muss ich bei einer Teilnahme tun? – Was geschieht mit mir bei einer Teilnahme?

- Wenn Sie sich entscheiden mitzumachen, werden Sie das Medikament Empagliflozin und ein Placebo (gleich aussehende Tablette ohne Wirkstoff) während jeweils 20 Tagen einnehmen. Die Reihenfolge wird zufällig festgelegt (sogenannte Randomisierung) und weder Sie noch das medizinische

INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HÔPITAL UNIVERSITAIRE DE BERNE
Universitätsklinik für Diabetologie, Endokrinologie, Ernährungsmedizin und Metabolismus

Betreuungspersonal wissen, ob Sie Medikament oder Placebo einnehmen (sogenannt doppelte Verblindung).

- Zu Beginn überprüfen wir Ihre Eignung zur Studienteilnahme, informieren Sie über den Studienablauf und holen Ihre schriftliche Einwilligung ein. Sie erhalten dann die erste Dose des Medikaments (Empagliflozin oder Placebo).
- Nach 20 Tagen werden Sie bei uns ein Frühstück einnehmen. Wir werden davor und danach Blut zur Messung des Blutzuckers und von Hormonen entnehmen. Dieser Besuch dauert ca. 3 Stunden.
- Nach einer Pause von 2-6 Wochen erhalten Sie das zweite Medikament. Nach wiederum 20 Tagen führen wir denselben Test mit Frühstück und regelmässigen Blutentnahmen bei Ihnen durch (Dauer wiederum ca. 3 Stunden)
- Während der Einnahme des Medikaments wird Ihr Zuckerverlauf mit einem Gerät, welches auf der Haut getragen wird, aufgezeichnet. Den Zeitpunkt der Mahlzeiten, welche Sie zu sich nehmen und allfällige Beschwerden dokumentieren Sie elektronisch.

Welcher Nutzen und welches Risiko sind damit verbunden?

Nutzen

- Sie tragen mit Ihrer Teilnahme zur Verfügbarkeit neuer Behandlungsmöglichkeiten von Unterzuckerung nach Magenbypass-Operationen bei.
- Durch ihre Teilnahme helfen Sie künftigen Patientinnen und Patienten.

Risiko und Belastung

- Empagliflozin ist zugelassen zur Behandlung von Diabetes und hat ein sehr günstiges Verträglichkeitsprofil.
- Bei Menschen mit Diabetes sind die häufigsten Nebenwirkungen vermehrtes Wasserlassen und Harnwegsinfekte.

Mit Ihrer Unterschrift am Ende des Dokuments bestätigen Sie, dass Sie freiwillig an der Studie teilnehmen und, dass Sie die Inhalte des gesamten Dokuments verstanden haben.

INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HÔPITAL UNIVERSITAIRE DE BERNE
Universitätsklinik für Diabetologie, Endokrinologie, Ernährungsmedizin und Metabolismus

Detaillierte Informationen

1. Ziel und Auswahl

Unser Forschungsprojekt bezeichnen wir in diesem Informationsschreiben als *Studie*. Wenn Sie an dieser Studie teilnehmen, sind Sie eine *Studienteilnehmerin* bzw. ein *Studienteilnehmer*.

Bevor ein Medikament bei einer Erkrankung angewendet wird, muss es bei Studienteilnehmern wissenschaftlich untersucht werden. Das Ziel dieser Studie ist es, den Nutzen einer neuen Behandlung bei Menschen, welche an Unterzuckerungen nach dem Essen (sog. „postprandialen Hypoglykämien“) als Folge einer Magenbypass-Operation leiden, zu untersuchen.
Bei dem Medikament handelt es sich um das Medikament Jardiance® (Wirkstoff: Empagliflozin), das in der Schweiz aktuell für die Behandlung von Patient*Innen mit Zuckerkrankheit (Diabetes) zugelassen ist. Daten aus einer kürzlich veröffentlichten Studie von Forschenden der Universität Basel legen nahe, dass die Einnahme von Empagliflozin im täglichen Leben von Patient*Innen nach Magenbypass-Operation Blutzuckerschwankungen und das Auftreten von Unterzuckerungen nach Mahlzeiten verringern kann. Empagliflozin hemmt die Zuckerwiederaufnahme in der Niere und verringert so den Blutzuckeranstieg nach der Einnahme zuckerhaltiger Speisen. Durch den geringeren Blutzuckeranstieg wird weniger Insulin (Blutzucker-senkendes Hormon) ausgeschüttet, womit das Risiko für Unterzuckerungen und Blutzuckerschwankungen kleiner wird. In der Studie verwenden wir die bei Diabetes-Patient*Innen zugelassene Dosis von 25 mg pro Tag. Bei gesunden Personen wurden Dosen bis zu 800 mg pro Tag getestet ohne dass Sicherheitsprobleme auftraten.

Wir fragen Sie an, da Sie an Unterzuckerungen nach dem Essen leiden,vor mehr als einem Jahr eine Magenbypass-Operation erhielten und Älter als 18 Jahre sind. Von der Teilnahme ausgeschlossen sind Personen, die nicht für die Einnahme von Empagliflozin (nach Ermessen des/der Prüfarztes/Prüfärztin) geeignet sind. Weitere Ausschlusskriterien sind komplizierte Harnwegsinfekte, Einschränkungen der Nierenfunktion, aktuelle oder geplante Schwangerschaft, Stillen oder die Einnahme von Medikamenten, die den Blutzucker während der Studienzeit beeinflussen.

2. Allgemeine Informationen

- Dieses Projekt wird mit insgesamt 22 Erwachsenen am Inselspital Bern durchgeführt.
  Es wird nach dem Zufallsprinzip entschieden (sogenannte Randomisierung), ob Sie zuerst mit Empagliflozin 25 mg oder Placebo (gleich aussehende Tablette ohne Wirkstoff) behandelt werden, oder umgekehrt. Alle Teilnehmer*Innen werden beiden Behandlungen unterzogen: eine Hälfte wird mit Empagliflozin starten, und danach Placebo erhalten, die andere Hälfte wird in umgekehrter Reihenfolge behandelt. Weder Sie noch Ihr medizinisches Betreuungsteam erfahren die Gruppenzuteilung (sogenannt doppelte Verblindung). Nur durch die Placebo-Kontrolle kann festgestellt werden, ob es Unterschiede zwischen dem spontanen Verlauf und der Behandlung mit Empagliflozin gibt. Beide Tabletten (Empagliflozin und Placebo) werden während jeweils 20 Tagen, mit einer Pause von 2-6 Wochen, einmal täglich eingenommen.
- Das Ansprechen auf die Therapie wird mit einem Mahlzeitentest an unserer Klinik am Tag 20 jeder Behandlungsphase untersucht. Dabei erhalten Sie ein Frühstück. Davor und danach werden regelmässige Blutentnahmen durchgeführt. Während jeder Behandlungsphase werden Sie ausserdem ein Messgerät zur fortlaufenden Messung des Zuckers (sogenanntes „kontinuierliches Glukosemessgerät“) auf der Haut tragen und die Einnahme von Mahlzeiten und allfällige Beschwerden elektronisch festhalten. Am Tag 19 jeder Behandlungsphase müssen Sie zudem eine 24-Stunden-Urinsammlung durchführen.
- Empagliflozin ist in der Schweiz zur Behandlung von Diabetes zugelassen. Aufgrund seiner Wirkungsweise wird vermutet, dass Empagliflozin auch bei Unterzuckerung nach Einnahme von Mahlzeiten nach z.B. einer Magenbypass-Operation wirken kann. Empagliflozin hat auch bei Menschen ohne Diabetes ein gutes Sicherheitsprofil.

- Die Studie wird so durchgeführt werden, wie es die Gesetze in der Schweiz vorschreiben. Ausserdem beachten wir alle international anerkannten Richtlinien. Die zuständige kantonale Ethikkommission und Swissmedic haben die Studie geprüft und bewilligt. Eine Beschreibung dieser Studie finden Sie auch auf der Internetseite des Bundesamtes für Gesundheit: www.kofam.ch.

3. Ablauf

Der Ablauf zur Teilnahme an der Studie ist in Abbildung 1 dargestellt.
Bei Ihrem ersten Besuch (Visite 0) prüfen wir Ihre Studieneignung, klären allfällige Fragen und holen - sofern Sie an der vorliegenden Studie teilnehmen möchten - Ihr schriftliches Einverständnis ein. Wenn Sie Medikamente einnehmen, die den Blutzucker beeinflussen aber an der Studie teilnehmen wollen, werden diese Medikamente für eine gewisse Zeit gestoppt. Dies erklärt Ihnen Ihr Prüfarzt/ Ihre Prüfärztin. Wir werden Ihnen die erste Flasche mit Medikament (entweder Empagliflozin oder Placebo) aushändigen und erklären Ihnen das Tragen des kontinuierlichen Glukosemessgeräts, wie Sie Mahlzeiten und Beschwerden elektronisch festhalten und die 24 Stunden-Urinsammlung vor dem zweiten Besuch (Visite 1).
Sie nehmen nun jeden Tag eine Tablette des Medikaments am Morgen ein. Am 19. Tag werden Sie beginnen, Ihren Urin für 24 Stunden zu sammeln. Am 20. Tag der Einnahme erscheinen Sie in nüchternem Zustand zur Visite 1 an unserer Klinik. Sie werden bei uns ein Frühstück einnehmen. Wir werden davor und danach Blut entnehmen um den Zucker im Blut und Hormone zu messen, welche Einfluss auf den Blutzucker haben. Pro Test werden wir 75 ml Blutentnehmen, was für Ihre Gesundheit unproblematisch ist (Vergleich: bei einer Blutspende werden 450-500ml Blut entnommen). Der Test dauert ca. 3 Stunden. Im Sammelurin, welchen Sie zur Visite mitbringen, messen wir die Zuckerausscheidung über die Niere. Die kontinuierliche Glukosemessung und das Erfassen der Mahlzeiten und Beschwerden dienen der Auswertung der Blutzuckerschwankungen und Beschwerden während der Einnahme des Medikaments. Am Schluss der Visite 1 erhalten Sie die 2. Flasche mit Medikament (entweder Empagliflozin oder Placebo). Nach einer Pause von 2-6 Wochen nehmen Sie erneut für täglich eine Tablette des Medikaments am Morgen für 20 Tage ein. Am Tag 20 erscheinen Sie zur Visite 2 an unserer Klinik. Die kontinuierliche Glukosemessung, das Festhalten von Mahlzeiten und Beschwerden sowie die Urinsammlung am Tag 19 der Tabletteneinnahme führen Sie unverändert durch. Der Ablauf von Visite 2 ist genau gleich wie jener von Visite 1.
Nach Visite 2 endet die Behandlung der Studie. Nach 2 Wochen werden Sie telefonisch zu Ihrem Gesundheitszustand befragt.

Es kann sein, dass wir Sie von der Studie vorzeitig ausschliessen müssen. Das kann deshalb geschehen, wenn bei ihnen Umstände auftreten, welche die weitere Teilnahme an der Studie verbieten, oder der Prüfarzt/die Prüfärztin der Meinung ist, dass eine weitere Teilnahme an der Studie Ihre Gesundheit gefährdet. In diesem Fall werden Sie zu ihrer Sicherheit nach 2 Wochen kontaktiert und gegebenenfalls an unserer Klinik untersucht. Bitte bringen Sie dann alle Medikamente und Materialien, welche wir Ihnen gegeben haben, zu uns zurück. Ihr Hausarzt/Ihre Hausärztin wird über die Studienteilnahme informiert werden.

4. Nutzen

Durch diese Studie werden wir wichtige Erkenntnisse zu neuen Behandlungsmöglichkeiten von postprandialen Hypoglykämien nach Magenbypass-Operation gewinnen. Diese sind von Nutzen für andere Personen, die dieselben Beschwerden haben.

5. Freiwilligkeit und Pflichten

Eine Teilnahme ist freiwillig. Wenn Sie nicht an dieser Studie teilnehmen oder später Ihre Teilnahme zurückziehen wollen, müssen Sie dies nicht begründen. Ihre medizinische Behandlung/Betreuung ist unabhängig von Ihrem Entscheid gewährleistet.

Wenn Sie an der Studie teilnehmen, müssen Sie bestimmte Regeln beachten. Dies ist notwendig für Ihre Sicherheit und Gesundheit. Wir werden Sie dabei bestmöglich unterstützen. Als Studienteilnehmende/r sind Sie verpflichtet,

- den medizinischen Anweisungen Ihres/Ihrer Prüfarztes/Prüfärztin zu folgen und sich an den Studienplan zu halten,
- in nüchternem Zustand zu den Visiten 1 und 2 zu erscheinen (das heisst, dass Sie ab Mitternacht nichts mehr essen und bei Bedarf nur mehr Wasser trinken). Das Medikament können Sie auch an den Tagen von Visite 1 und 2 jeweils am Morgen mit einem Schluck Wasser einnehmen. Das gilt auch für Ihre allfälligen weiteren Medikamente.
- bei Visite 1 und 2 die Flasche mit Medikament mitzubringen.
- Ihren Prüfarzt/Ihre Prüfärztin über Änderungen Ihres Gesundheitszustandes zu informieren. Melden Sie insbesondere auch neue Symptome, neue Beschwerden und Änderungen in Ihrem Befinden (auch nach Studienende/-abbruch, z.B. bis die unerwünschte Wirkung abklingt);
- gleichzeitige Behandlungen und Therapien, denen sie sich während der Teilnahme an der Studie bei einem anderen Arzt/einer anderen Ärztin unterziehen möchten, erst mit Ihrem Prüfarzt/Ihrer Prüfärztin zu besprechen, und
- Ihren Prüfarzt/Ihre Prüfärztin immer über die Einnahme von zusätzlichen Medikamenten zu informieren. Nennen Sie bitte alle Medikamente, auch solche, die Sie selbst gekauft haben, für die Sie kein Rezept brauchen oder alternativmedizinische Präparate.

6. Risiken und Belastungen

Empagliflozin hat sich während der letzten Jahre als ein Medikament mit sehr guter Verträglichkeit erwiesen. Bei Menschen ohne Diabetes wurden hohe Dosen bis zu 800 mg pro Tag getestet, mit guter Verträglichkeit.

Folgende unerwünschte Wirkungen von Empagliflozin werden bei Personen mit Diabetes oft beobachtet:

- Harnwegsinfektionen, insbesondere Pilzinfektionen. Diese sind in der Regel harmlos und lassen sich gut behandeln.
- Bei Diabetes-Patienten mit fehlender oder verringerter eigener Insulinproduktion liegt ein erhöhtes Risiko für die Ketoazidose vor. Ketoazidose bedeutet, dass sich saure Stoffe im Blut ansammeln. Bei Personen ohne Diabetes sind keine Fälle von Ketoazidose in Zusammenhang mit Empagliflozin bekannt. Bei Personen mit Unterzuckerungen nach Magenbypass-Operation ohne Diabetes ist eine Ketoazidose sehr unwahrscheinlich.
- Bei gleichzeitiger Einnahme von anderen Diabetes-Medikamenten (Ausschlusskriterium für Studienteilnahme), die selbst zu Unterzuckerungen führen können (v.a. Insulin), ist das Risiko für Unterzuckerungen erhöht.

Unabhängig von der Einnahme des Medikaments bestehen folgende weiteren Risiken:

- Das Tragen des kontinuierlichen Glukosemessgeräts kann zu Hautreizungen führen.
- Die Einlage der Venenverweilkanüle für die Blutentnahmen an Visite 1 und 2 kann zu Blutergüssen und sehr selten zu Venenentzündungen führen.
- Das kontinuierliche Glukosemessgerät muss im Falle bestimmter Untersuchungen (vor allem bildgebender Verfahren) entfernt wegen. Bitte informieren Sie Ihren Prüfarzt/ Ihre Prüfärztin, wenn bei Ihnen während der Studienzeit eine bildgebende Untersuchung geplant wird.

Für Frauen, die schwanger werden können

Es liegen nur sehr begrenzte Erfahrungen über die Anwendung von Empagliflozin bei schwangeren Frauen vor. Studien an Tieren ergaben keine Hinweise auf Schäden der Fruchtbarkeit oder der Entwicklung des Nachwuchses im Mutterleib. Aufgrund möglicher Auswirkungen auf die Entwicklung des Kindes beim Menschen ist die Anwendung von Empagliflozin während der Schwangerschaft zu

INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HÔPITAL UNIVERSITAIRE DE BERNE
Universitätsklinik für Diabetologie, Endokrinologie, Ernährungsmedizin und Metabolismus

vermeiden. Wir führen deswegen vor jeder Behandlungsphase bei Frauen im gebärfähigen Alter einen Schwangerschaftstest im Urin durch. Frauen im gebärfähigen Alter müssen während der gesamten Behandlung eine zuverlässige Verhütungsmethode anwenden (hormonelle Methode wie Pille oder Spirale).
Sollten Sie während der Studie trotzdem schwanger werden, müssen Sie Ihren Prüfarzt/Ihre Prüfärztin sofort informieren und dürfen nicht weiter an der Studie teilnehmen. In diesem Fall werden Sie gebeten, Angaben über den Verlauf und den Ausgang der Schwangerschaft zu machen. Der Prüfarzt/die Prüfärztin wird mit Ihnen das weitere Vorgehen besprechen.
Es gibt keine Informationen darüber, ob Empagliflozin beim Menschen in die Muttermilch übergeht. Daten aus Studien an Tieren zeigten, dass Empagliflozin in die Milch übergeht und unerwünschte Wirkungen auf die Entwicklung des Nachwuchses nach der Geburt hat. Ein Risiko für das Neugeborene/Kind beim Menschen kann nicht ausgeschlossen werden. Das Stillen muss – wenn eine Studienteilnahme dennoch erwünscht ist - während der Studienteilnahme unterbrochen werden.

7. Alternativen

Die Teilnahme an der Studie ist mit Chancen und Risiken verbunden. Die Möglichkeiten zur Behandlung postprandialer Hypoglykämien nach Magenbypass-Operation sind begrenzt und es gibt keine zugelassenen Medikamente. Ernährungsumstellungen (v.a. das Vermeiden von Zucker in der Nahrung) können sehr effektiv sein, sind aber nicht immer ausreichend und im Alltag oft schwer umsetzbar. Der Wirkstoff „Acarbose“ hemmt die Zucker-Aufnahme im Dünndarm. Die Wirksamkeit gegen postprandiale Hypoglykämien wurde in Studien nachgewiesen. Allerdings wird Acarbose oft nicht vertragen (Blähungen, Bauchkrämpfe) und die Einnahme vor jeder Mahlzeit ist nicht anwenderfreundlich. Acarbose ist zudem in der Schweiz nicht mehr erhältlich. Weitere Substanzen sind sehr teuer, können ernste Nebenwirkungen haben und wurden bisher nur in Einzelfällen eingesetzt. Ihr Prüfarzt/ Ihre Prüfärztin wird Sie im Gespräch darüber informieren.

8. Ergebnisse

Es gibt

1. Ergebnisse der Studie, die Sie direkt betreffen,
2. Ergebnisse der Studie, die zufällig entstehen (sogenannte Zufallsergebnisse)
3. End-Ergebnisse der gesamten Studie.

Zu 1: Ihr Prüfarzt/ Ihre Prüfärztin wird Sie im Verlauf der Studie über alle für Sie persönlich wichtigen, neuen Ergebnisse und Erkenntnisse informieren. Sie werden mündlich und schriftlich informiert und können dann erneut entscheiden, ob Sie an der Studie weiterhin teilnehmen möchten.

Zu 2: Zufallsbefunde sind sogenannte „Begleit-Ergebnisse“, also Ergebnisse, nach denen man nicht gesucht hat, sondern die zufällig gefunden werden. Im Falle unserer Studie können dies Befunde aus Blut- oder Urinsammlungen sein.
Bei Zufallsbefunden werden Sie informiert, wenn diese Befunde relevant für Ihre Gesundheit sind. Das bedeutet, dass solche Befunde Ihnen dann mitgeteilt werden, wenn man zufällig eine bislang nicht bekannte Erkrankung festgestellt hat oder eine noch nicht aufgetretene Erkrankung durch Vorbeugung verhindern kann. Wenn Sie darüber nicht informiert werden wollen, sprechen Sie bitte mit Ihrem Prüfarzt/ Ihrer Prüfärztin.

Zu 3: Ihr Prüfarzt/ Ihre Prüfärztin kann Ihnen am Ende der Studie eine Zusammenfassung der Gesamtergebnisse zukommen lassen.

9. Vertraulichkeit von Daten und Proben

Im Rahmen der Studie werden persönliche und medizinische Daten erhoben. Nur wenige Fachleute sehen Ihre unverschlüsselten Daten, und auch nur, um Aufgaben innerhalb der Studie zu erfüllen.

INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HÔPITAL UNIVERSITAIRE DE BERNE
Universitätsklinik für Diabetologie, Endokrinologie, Ernährungsmedizin und Metabolismus

Bei der Datenerfassung für Studienzwecke werden die Daten verschlüsselt. Verschlüsselung bedeutet, dass alle Daten, mit der man Sie erkennen könnte (z.B. Name, Geburtsdatum), durch einen Code (Schlüssel) ersetzt werden. Dadurch können Personen, die den Schlüssel nicht kennen, keine Rückschlüsse auf Ihre Person ziehen. Innerhalb des Inselspitals können die Daten durch berechtigte Personen auch ohne Verschlüsselung eingesehen werden. Die Schlüssel-Liste bleibt immer im Spital. Im Falle einer Veröffentlichung können die zusammengefassten Daten nicht auf Sie als Person zurückgeführt werden. Ihr Name erscheint niemals im Internet oder in einer Veröffentlichung. Manchmal verlangt eine Zeitschrift die Einreichung einzelner Daten (sogenannte Rohdaten) zur Veröffentlichung. Wenn persönliche Daten übermittelt werden müssen, sind diese immer verschlüsselt und es kann kein Rückschluss auf Ihre Person gezogen werden. Alle Personen, die im Rahmen des Projekts Zugang zu Ihren Daten haben, unterliegen der Schweigepflicht. Die datenschutzrechtlichen Bestimmungen werden eingehalten und Sie haben als Teilnehmer*In jederzeit das Recht, Ihre Daten einzusehen.
Ihre verschlüsselten Daten und Proben werden in einer sicheren Studiendatenbank oder Biobank an der Universitätsklinik für Diabetologie, Endokrinologie, Ernährungsmedizin und Metabolismus (UDEM) am Inselspital Bern für mindestens 10 Jahre gespeichert bzw. gelagert. Es ist möglich, dass Ihre Daten und Proben in Zukunft für neue, noch nicht definierte wissenschaftliche Projekte verwendet werden. Zu diesem Zweck können sie an eine andere Datenbank in der Schweiz oder im Ausland gesendet werden. Die Studienleiterin muss sich vergewissern, dass das Zielland einen datenschutzrechtlichen Standard gewährleistet, der dem in der Schweiz garantierten Standard gleichwertig ist. Für diese weitere Verwendung bitten wir Sie, ganz am Ende dieses Dokuments eine weitere Einverständniserklärung zu unterschreiben. Die Projektleitung ist für die Einhaltung der nationalen und internationalen Datenschutzbestimmungen und für die ordnungsgemäße Aufbewahrung der Daten und Proben verantwortlich. Ein gleichwertiges Datenschutzniveau ist im Ausland gewährleistet.
Diese Studie kann von der zuständigen Ethikkommission, der Arzneimittelbehörde Swissmedic oder von der Einrichtung, die die Studie durchführt, geprüft werden. Für diese Prüfungen muss die Studienleiterin möglicherweise Ihre persönlichen und medizinischen Daten offenlegen. Alle Personen müssen absolute Vertraulichkeit wahren. Wir werden alle datenschutzrechtlichen Bestimmungen einhalten und Ihren Namen in keiner Publikation oder im Internet bekannt geben. Es besteht die Möglichkeit, dass wir Ihren Hausarzt kontaktieren, um Informationen über Ihren medizinischen Zustand zu erhalten.

10. Rücktritt

Sie können jederzeit von der Studie zurücktreten. Die bis dahin erhobenen Daten und Proben werden in diesem Fall allerdings noch verschlüsselt ausgewertet. Im Falle eines Rücktritts bleiben Ihre Daten und Proben weiterhin verschlüsselt aufbewahrt. Überlegen Sie sich bitte, ob Sie damit einverstanden sind, bevor Sie bei der Studie mitmachen.

11. Entschädigung

Wenn Sie an dieser Studie teilnehmen, erhalten Sie dafür eine Entschädigung von CHF 300.-.
Auslagen wie Reisespesen, die durch die Teilnahme bedingt sind, werden wir Ihnen vergüten.
Es entstehen Ihnen oder Ihrer Krankenkasse keine Kosten durch die Teilnahme.

12. Haftung

Das Inselspital, welches für die Durchführung der Studie verantwortlich ist, haftet für Schäden, die Ihnen im Zusammenhang mit dem Medikament und/oder den Forschungshandlungen (z.B. Untersuchungen) entstehen könnten. Die Voraussetzungen und das Vorgehen dazu sind gesetzlich geregelt. Das Inselspital Bern hat daher bei der Zürich Versicherungs-Gesellschaft AG eine Versicherung abgeschlossen, um im Schadensfall für die Haftung aufkommen zu können.

INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HÔPITAL UNIVERSITAIRE DE BERNE
Universitätsklinik für Diabetologie, Endokrinologie, Ernährungsmedizin und Metabolismus

Sollten Sie durch die Teilnahme an dieser Studie einen Schaden erleiden, so wenden Sie sich bitte an Ihren Prüfarzt/ Ihre Prüfärztin oder an das oben erwähnte Versicherungsunternehmen (Zürich Versicherungs-Gesellschaft AG, Mythenquai 2, 8002 Zürich).

13. Finanzierung

Die Studie wird durch den Schweizerischen National Fonds zur Förderung der wissenschaftlichen Forschung finanziert. Das Medikament wird von Boehringer Ingelheim zur Verfügung gestellt.

14. Kontaktperson(en)

Sie dürfen jederzeit Fragen zur Studienteilnahme stellen. Auch bei Unsicherheiten oder Notfällen, die während der Studie oder danach auftreten, wenden Sie sich bitte an:

Prof. Dr. med. et phil. Lia Bally (verantwortliche Ärztin/Prüferin)
Leiterin Forschung, Fachbereichsleiterin Ernährung und Metabolismus
Universitätsklinik für Diabetologie, Endokrinologie, Ernährungsmedizin und Metabolismus
Inselspital, 3010 Bern
lia.bally@insel.ch
031 632 36 77

Während der Studie können Sie uns jederzeit unter den folgenden Telefonnummern erreichen:

Kontakt für allgemeine Fragen

Studienarzt: Antonio Ferreira
Telefon: +41 31 66 4 23 55
E-mail: antonio.ferreira@insel.ch

24/7 NOTFALLKONTAKT

1. Studienarzt: Antonio Ferreira
   Telefon: +41 31 66 4 23 55
2. Studienarzt: Andreas Melmer
   Telefon: +41 78 705 49 53
3. Studienleiterin: Lia Bally
   Telefon: +41 31 63 2 36 77

INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HÔPITAL UNIVERSITAIRE DE BERNE
Universitätsklinik für Diabetologie, Endokrinologie, Ernährungsmedizin und Metabolismus

Einwilligungserklärung

Schriftliche Einwilligungserklärung zur Teilnahme an einer klinischen Studie
Bitte lesen Sie dieses Formular sorgfältig durch. Bitte fragen Sie, wenn Sie etwas nicht verstehen oder wissen möchten. Für die Teilnahme ist Ihre schriftliche Einwilligung notwendig.

BASEC-Nummer (nach Einreichung):	2021-01187
Titel der Studie (wissenschaftlich und Laiensprache):	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) Wirkung von Empagliflozin auf Unterzuckerungen nach Magenbypass-Operation eine randomisiert-kontrollierte Doppelblind-Studie
Verantwortliche Institution (Sponsor mit Adresse):	Universitätsklinik für Diabetologie, Endokrinologie, Ernährungsmedizin und Metabolismus Freiburgstrasse 15, 3010 Bern
Ort der Durchführung:	Inselspital
Prüfärztin/Prüfarzt am Studienort: Name und Vorname in Druckbuchstaben:	Prof. Dr. med. et. phil. Lia Bally
Teilnehmerin/Teilnehmer: Name und Vorname in Druckbuchstaben: Geburtsdatum:	

- Ich wurde von der unterzeichnenden Prüfärztin/dem unterzeichnenden Prüfarzt mündlich und schriftlich über den Zweck, den Ablauf der Studie mit möglichen Vor- und Nachteilen sowie über eventuelle Risiken informiert.
- Ich nehme an dieser Studie freiwillig teil und akzeptiere den Inhalt der mir ausgehändigten schriftlichen Information. Ich hatte genügend Zeit, meine Entscheidung zu treffen.
- Meine Fragen im Zusammenhang mit der Teilnahme an dieser Studie sind mir beantwortet worden. Ich behalte die schriftliche Information und erhalte eine Kopie meiner schriftlichen Einwilligungserklärung.
- Ich wurde über mögliche Alternativen zur Studie, z.B. andere Behandlungsverfahren aufgeklärt.
- Ich bin einverstanden, dass meine Hausärztin/mein Hausarzt über meine Teilnahme an der Studie informiert wird.
- Im Fall einer Weiterbehandlung ausserhalb des Prüfzentrums ermächtige ich meine nachbehandelnden Ärztinnen und Ärzte, meine für die Studie relevanten Daten der Prüfärztin/dem Prüfarzt zu übermitteln.
- Ich bin einverstanden, dass die zuständigen Fachleute des Sponsors, der zuständigen Ethikkommission und der Arzneimittelbehörde Swissmedic zu Prüf- und Kontrollzwecken in

INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HÔPITAL UNIVERSITAIRE DE BERNE
Universitätsklinik für Diabetologie, Endokrinologie, Ernährungsmedizin und Metabolismus

meine unverschlüsselten Daten Einsicht nehmen dürfen, jedoch unter strikter Einhaltung der Vertraulichkeit.

- Bei Ergebnissen oder Zufallsbefunden, die direkt meine Gesundheit betreffen, werde ich informiert. Wenn ich das nicht wünsche, informiere ich meine Prüfärztin/ meinen Prüfarzt.
- Ich kann jederzeit und ohne Angabe von Gründen von der Studienteilnahme zurücktreten. Meine weitere medizinische Behandlung ist unabhängig von der Studienteilnahme gewährleistet. Die bis zum Rücktritt erhobenen Daten und Proben werden noch im Rahmen der Studie ausgewertet.
- Ich bin darüber informiert, dass das Inselspital eine Versicherung abgeschlossen hat, welche Schäden, die auf das Forschungsprojekt zurückzuführen sind, deckt.
- Ich bin mir bewusst, dass die in der Informationsschrift genannten Pflichten einzuhalten sind. Im Interesse meiner Gesundheit kann mich die Prüfärztin/der Prüfarzt jederzeit von der Studie ausschliessen.

Ort, Datum	Unterschrift Teilnehmerin/Teilnehmer

Bestätigung der Prüfärztin/des Prüfarztes: Hiermit bestätige ich, dass ich dieser Teilnehmerin/diesem Teilnehmer Wesen, Bedeutung und Tragweite der Studie erläutert habe. Ich versichere, alle im Zusammenhang mit dieser Studie stehenden Verpflichtungen gemäss in der Schweiz geltenden Rechts zu erfüllen. Sollte ich im Verlauf der Studie von Aspekten erfahren, welche die Bereitschaft der Teilnehmerin/des Teilnehmers zur Studienteilnahme beeinflussen könnten, werde ich sie/ihn umgehend darüber informieren.

Ort, Datum	Name und Vorname der Prüfärztin/des Prüfarztes in Druckbuchstaben Unterschrift der Prüfärztin/des Prüfarztes

Inselspital, Universitätsklinik für Diabetologie, Endokrinologie, Ernährungsmedizin und Metabolismus (UDEM), CH-3010 Bern

INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HÔPITAL UNIVERSITAIRE DE BERNE
Universitätsklinik für Diabetologie, Endokrinologie, Ernährungsmedizin und Metabolismus

Einwilligungserklärung für Weiterverwendung von Daten und biologischem Material in verschlüsselter Form

BASEC-Nummer (nach Einreichung):	2021-01187
Titel der Studie (wissenschaftlich und Laiensprache):	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) Wirkung von Empagliflozin auf Unterzuckerungen nach Magenbypass-Operation eine randomisiert-kontrollierte Doppelblind-Studie
Teilnehmerin/Teilnehmer: Name und Vorname in Druckbuchstaben: Geburtsdatum:	

Ich erlaube, dass meine verschlüsselten Daten und Proben aus dieser Studie für die medizinische Forschung weiterverwendet werden dürfen. Die Proben werden in einer Biobank am Inselspital Bern für zukünftige, noch nicht näher definierte Forschungsprojekte auf unbestimmte Zeitdauer verwendet.

Ich habe verstanden, dass die Proben verschlüsselt sind und der Schüssel sicher aufbewahrt wird. Die Daten und Proben können im In- und Ausland an andere Daten- und Biobanken zur Analyse gesendet werden, wenn diese dieselben Standards wie in der Schweiz einhalten. Alle rechtlichen Vorgaben zum Datenschutz werden eingehalten.

Ich entscheide freiwillig und kann diesen Entscheid zu jedem Zeitpunkt wiederzurücknehmen. Wenn ich zurücktrete, bleiben die Daten und Proben verschlüsselt, da eine Anonymisierung im vorliegenden Projekt nur mit einem unverhältnismäßig großen Aufwand an Zeit, Kosten und Arbeitskraft möglich wäre. Ich informiere lediglich meine Prüfärztin/meinen Prüfarzt und muss diesen Entscheid nicht begründen. Nach dem Wiederruf werden meine Daten und Proben für neue Forschungsprojekte nicht mehr zur Verführung gestellt.

Normalerweise werden alle Daten und Proben gesamthaft ausgewertet und die Ergebnisse zusammenfassend publiziert. Sollte sich ein für meine Gesundheit wichtiges Ergebnis ergeben, ist es möglich, dass ich kontaktiert werde. Wenn ich das nicht wünsche, teile ich dies meiner Prüfärztin/meinem Prüfarzt mit.

Wenn Ergebnisse aus den Daten und Proben kommerzialisiert werden, habe ich keinen Anspruch auf Anteil an der kommerziellen Nutzung.

Ort, Datum	Unterschrift Teilnehmerin/Teilnehmer

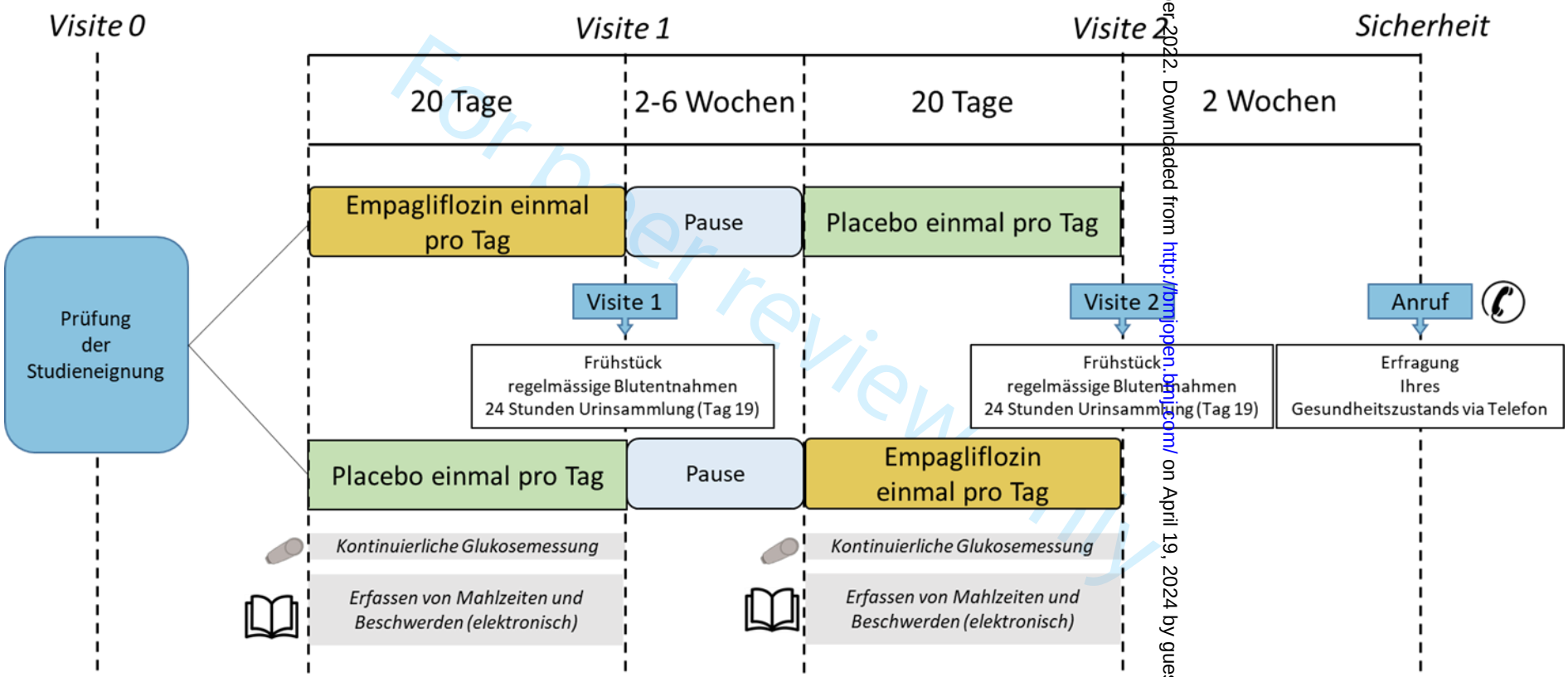
INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HÔPITAL UNIVERSITAIRE DE BERNE
Universitätsklinik für Diabetologie, Endokrinologie, Ernährungsmedizin und Metabolismus

Bestätigung der Prüfärztin/des Prüfarztes: Hiermit bestätige ich, dass ich dieser Teilnehmerin/diesem Teilnehmer Wesen, Bedeutung und Tragweite der Weiterverwendung von Proben und/oder Daten erläutert habe.

Ort, Datum	Name und Vorname der Prüfärztin/des Prüfarztes /der Prüfperson in Druckbuchstaben Unterschrift der Prüfärztin/des Prüfarztes/der Prüfperson

INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HÔPITAL UNIVERSITAIRE DE BERNE
Universitätsklinik für Diabetologie, Endokrinologie, Ernährungsmedizin und Metabolismus

Abbildung 1: Studienablauf



Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	Protocol V1 29.12.2021
Funding	#4	Sources and types of financial, material, and other support	Page 17

Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	Page 17
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	Page 1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Page 17
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Page 17
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 4-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	Page 4-6
Objectives	#7	Specific objectives or hypotheses	Page 6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	Page 9
Methods: Participants,			

interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 9-12
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 10
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 9
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	Page 9-12
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	Page 9-12
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 9-12
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 7-8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Page 9

Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 12
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 10
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 12
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Page 9-12
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 17
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 11
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Page 11
Methods: Data collection, management, and analysis			

Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 11-15
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 9-12
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 12-15
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 12-15
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 12-15
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 12-15
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the	N/A

		protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Page 12-15
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page 12-15
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 12-15
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	Page 16/17
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 16/17
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 15
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 16/17

Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 16/17
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page 16/17
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Available upon request
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A