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

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SCHOLARONE™
Manuscripts

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3 **Randomized, double-blind, placebo-controlled crossover trial assessing the impact of the**
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5 **SGLT2 inhibitor empagliflozin on postprandial hypoglycaemia after gastric bypass**
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9 DEEP-EMPA TRIAL
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12 Clinical Study Protocol
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Abstract

Introduction:

Postprandial hypoglycaemia after gastric bypass surgery (also known as postbariatric hypoglycaemia or PBH) is an increasingly encountered clinical problem. PBH is 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 $< 3.0\text{ mmol/L}$). 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 \pm 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

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3 results are expected in the first quarter of 2023 and will be disseminated via peer-reviewed
4 publications and presented at national and international conferences.
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10 **Trial registration:**
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12 This trial is registered with Clinicaltrial.gov (NCT05057819) and the Swiss National Clinical
13 Trials Portal (SNCTP000004622).
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17 **Strengths and limitations of this study**
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- 24 - First study that investigates the effect of empagliflozin 25mg on glycaemic variability
25 and hypoglycaemia burden in patients with PBH
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27 - Randomized, double-blind, placebo-controlled, crossover study design
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29 - Preliminary data will be key to establish the relevance for larger and longer trials
30 assessing the efficacy of empagliflozin 25mg in reducing PBH in unrestricted daily
31 living
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33 - Single-site design and short time-frame may limit applicability of findings to different
34 contexts
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48 **Keywords:**
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50 Postbariatric hypoglycaemia, PBH, Gastric bypass surgery, SGLT2 inhibitor, Empagliflozin
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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

1
2 calcium channel blockers. These medications are limited by poor tolerability, inconvenient
3 mode of administration, high costs or restricted availability (e.g. acarbose no longer available
4 on the Swiss market) [7, 15].
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7 In a proof-of-concept study, a single dose of 10 mg empagliflozin was administered to 12
8 patients with PBH and significantly lowered the proportion of patients experiencing
9 hypoglycaemia during a standardised mixed meal tolerance test compared to placebo (2 vs. 7
10 translating into a 74% risk reduction) [16]. Empagliflozin is an inhibitor of the sodium-glucose
11 cotransporter 2 (SGLT2) [17]. SGLT2 resides in the brush border membrane of proximal
12 tubular cells in the kidney and reabsorbs ~90 % of glucose filtered at the glomerulus [18].
13 SGLT2 inhibitors block the physiological glucose reabsorption in the proximal tubule from the
14 glomerular filtrate, thereby reducing postprandial hyperglycaemia through increased urinary
15 glucose excretion. Additionally, glucosuria produced by SGLT2 inhibition stimulates
16 endogenous glucose production, which is accompanied by an increase in plasma glucagon
17 levels [19-21]. Empagliflozin 10 mg or 25 mg once daily is approved for the treatment of type
18 2 diabetes. In healthy, non-diabetic, normoglycaemic volunteers, a dose of 25 mg once daily
19 was more effective in inducing glucosuria than 10 mg. In addition to improved glucose control,
20 empagliflozin was shown to decrease cardiovascular mortality, death from any cause,
21 hospitalizations for heart failure, decline kidney function and need for renal replacement
22 therapy in patients with type 2 diabetes [22-24].
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25 As far as safety is concerned, therapy with SGLT2 inhibitors is generally well tolerated. An
26 increased incidence of genital infections and (although rare) euglycaemic ketoacidosis are
27 known side effects. The latter is mainly observed in patients with type 1 diabetes and less
28 frequently in those with type 2 diabetes [17]. No cases of euglycaemic ketoacidosis in
29 individuals without diabetes treated with SGLT2 inhibitors have been reported.
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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 $\geq 30\text{g}/24\text{h}$ and $< 30\text{g}/24\text{h}$) 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

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2 intake until the end of the respective period.
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- 5 - Further outcomes will be assessed during visit 1 and 2 (mixed meal tolerance test) and
6 during daily living using records of symptoms and nutritional intake. Logging of
7 symptoms and nutritional intake will be done using an electronic diary.
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15 **Study design**

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17 The DEEP-Empa trial is an investigator-initiated randomized, double-blind, placebo-
18 controlled, crossover, single-centre study. Twenty-two participants will be randomized in equal
19 proportions into two groups (11 participants per group). In one group, 25 mg once daily
20 empagliflozin, the investigational medicinal product (IMP), will be given as the first treatment,
21 and a placebo in a form identical to empagliflozin as the second treatment. The other group
22 receives the same treatments in the reverse sequence. Study duration will be 2x20 days with a
23 randomized crossover allocation and an interspersed wash-out period of 2-6 weeks (Figure 1).
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35 **Study population**

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37 Eligible population consists of post-bariatric surgery patients, 18 years or older, who underwent
38 RYGB ≥ 1 year ago, and with biochemically confirmed postprandial hypoglycaemia defined as
39 plasma or sensor glucose measurement of <3.0mmol/L within the last three months before
40 recruitment. This threshold has been recognized by the International Hypoglycaemia Study
41 Group as clinically important hypoglycaemia due its association with neuroglycopenic
42 symptoms and adverse health effects [25]. Based on findings of a recent study, the threshold of
43 3.0mmol/L irrespective of the presence of neuroglycopenic symptoms was proposed to signify
44 clinically important hypoglycaemia specifically in the PBH population [8]. Recruitment occurs
45 via local advertisements and referrals from internal and external bariatric physicians. Written
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2 informed consent will be obtained before any study-related procedures. Study participation will
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4 be reimbursed for their efforts and time (CHF 300 plus study-related travel costs).
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10 Exclusion criteria:

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12 I. Diabetes on anti-diabetic treatment (insulin and/or non-insulin agents);
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14 II. Chronic kidney disease (defined as CKD-EPI eGFR < 60 mL/min per 1.73 m² body
15 surface area);
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17 III. Genito-urinary infection, if not treated successfully;
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19 IV. Pregnant and lactating women (urine pregnancy test to be performed for women of
20 childbearing potential [defined as women who are not surgically sterilized/
21 hysterectomized, and/ or who are postmenopausal for less than 12 months]) or women
22 of childbearing potential that refuse to use an effective contraceptive method [birth
23 control pill or IUD]);
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25 V. Inability to understand and follow the protocol;
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27 VI. Known allergy to the study drug;
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29 VII. Participation in another interventional clinical trial overlapping with the current trial
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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

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3 Eligible individuals will be randomized in equal proportions to 20 days 25 mg empagliflozin
4 followed by 20 days of placebo or vice-versa, taken once daily per os in the morning. Placebo
5 will be administered in a form identical to empagliflozin. Before randomization, participants
6 will attend a baseline visit (see Figure 1). Participants will remain on the assigned IMP/placebo
7 for 20 days. During the last day of treatment, participants will perform a 24h urine collection
8 and the following day attend the clinical research facility for a mixed meal tolerance test.
9 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
11 performed. Additionally, ketone levels (3-beta-hydroxybutyrate) will be assessed at baseline
12 and 30 min, 60 min following mixed-meal ingestion using a point-of-care device. The
13 standardised meal will consist of a typical solid breakfast (545kcal, 73g of carbohydrates, 22g
14 of fat and 12g of protein). The two study periods will be separated by a wash out period of 2-6
15 weeks. During the two 20 days periods, participants will be fitted with a blinded continuous
16 glucose monitor (Dexcom G6) and record symptoms and carbohydrate intake (semiquantitative,
17 e.g. ≥ 30 vs. < 30 g) in an electronic diary. The same diary will be also used to monitor adherence
18 to IMP/placebo. Two weeks after completion of the second treatment, participants will receive
19 a phone call to inquire about a general well-being and safety events.
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Statistical methods

Sample size

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46 The sample size was calculated based on the primary outcome. In a preliminary study involving
47 a sample of 12 patients with PBH, the mean paired-difference (empagliflozin - Placebo) of the
48 decrease in plasma glucose following a mixed-meal test was -1.46mmol/L (SD 0.31mmol/L).
49 With a sample size of 17 participants, the study would detect a mean paired-difference of
50 0.3mmol/L (this corresponds to an effect size of 0.75 with the assumption of a within participant
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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 accidentally in this trial), subjects that did not receive the treatment in the randomised sequence or subjects that did not comply with the intervention. A sensitivity analysis, done based on the per-protocol (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

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3 intake of the allocated capsule; or 2) more than four missed tablets (i.e. to be compliant, patients
4 must take at least 16 tablets); or 3) missed intake on day of visit 1 or 2.
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12 Primary Analysis

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14 Linear mixed effects model will be used for the statistical analysis. The mixed effects model
15 will contain the treatment and period as fixed effects to adjust for any period effects, and a
16 random effect for participants to account for within-participant correlation of repeated
17 measurements. Residual values will be assessed for normality using the Shapiro-Wilk test.
18 Transformations to normality for variables not fulfilling normality assumptions will be
19 considered (e.g. log, Box-Cox etc.). All primary and secondary endpoints will be analysed using
20 this approach. We will notably not formally test for possible carry-over effects for the following
21 reasons: 1) the long wash out period accounts for this by design and 2) such gate-keeping tests
22 lead to inflated type I errors.

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30 Mean \pm SD or summary statistics appropriate to the variable type will be reported for the
31 primary and secondary efficacy outcomes for the two treatments. Results from statistical
32 analyses will be presented as paired-differences \pm SD along with 95 % confidences intervals. A
33 two-sided p-value will be reported and a p-value <0.05 will be considered statistically
34 significant.

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48 **Statistical interim analysis**

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50 No interim analysis is planned.

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60 **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 ClinicalTrials.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

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3 first results are expected in Q1 of 2023. No publications containing results of this study have
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5 already been published or submitted to any journal.
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10 ***Consent for publication***
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12 Not applicable.
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17 ***Availability of data and materials***
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19 Datasets generated during the study will be made available upon request.
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24 ***Competing interests***
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26 Authors declare no competing interests. Boehringer Ingelheim provides the IMP. Boehringer
27
28 Ingelheim will have the right to comment on any manuscript derived from this study but will
29 not be allowed to interfere in the process of publishing results in any form deemed appropriate
30 by the investigators.
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39
40 The study is fully supported by the Swiss National Science Foundation (PCEGP3_186978/1).
41
42 The trial will also receive intramural support of the Bern University Hospital for local laboratory
43 analyses.
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49 ***Author's contributions***
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51 LB is the Sponsor-investigator of the trial and procured funding. LB and DH conceived the
52 study. LB, DH and AM wrote the study protocol and registered the study. LB, DH and CTN
53 wrote the statistical analysis plan. LB, DH and AF coordinate the study. LB and AF are involved
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3 in the recruitment of patients and patient care. LB, AF, AE drafted the first protocol manuscript.
4
5 All authors contributed to the manuscript and all authors read and approved the final version.
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31 **References**
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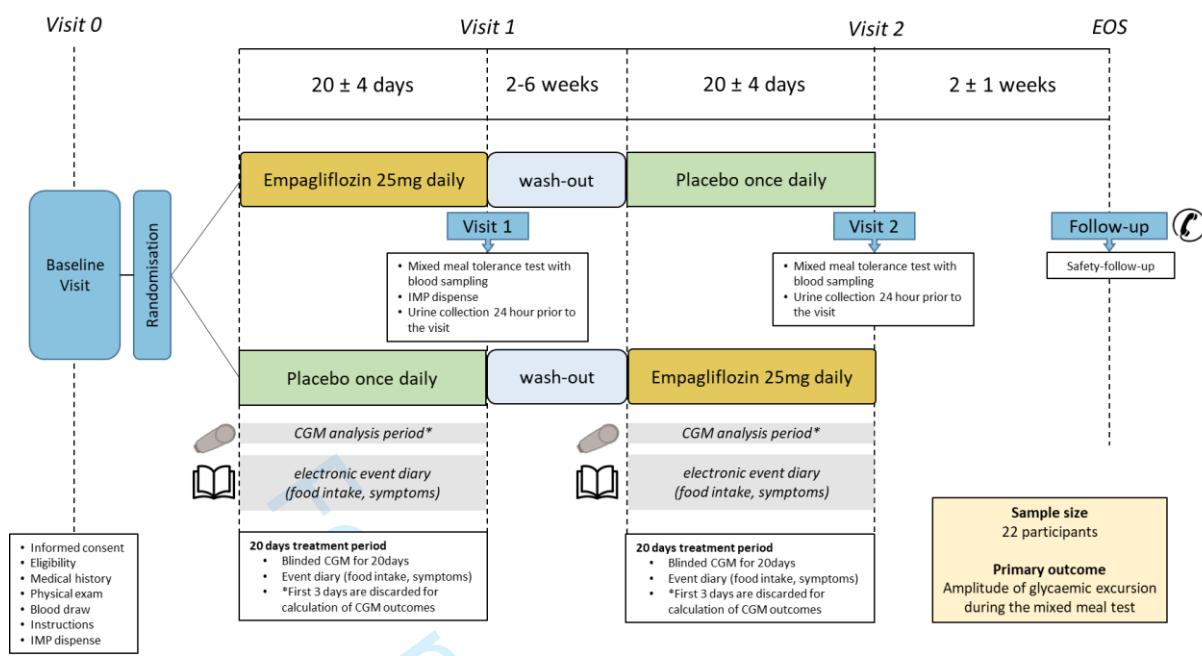
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Figures

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

For peer review only



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 SPIRIT reporting guidelines, and cite them as:

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

1	Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	Page 17
2				
3	Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	Page 1
4				
5	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
6				
7	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
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33	Introduction			
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35	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
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42	Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	Page 4-6
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47	Objectives	#7	Specific objectives or hypotheses	Page 6
48				
49	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
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56	Methods:			
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58	Participants,			
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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: adherence	#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

1	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
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8	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 10
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12	Methods:			
13	Assignment of interventions (for controlled trials)			
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18	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
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30	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
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38	Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 17
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43	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 11
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48	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
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54	Methods: Data collection, management, and analysis			
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1	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
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14	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
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20	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
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30	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
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37	Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 12-15
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41	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
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48	Methods:			
49	Monitoring			
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51	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
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1	2	3	protocol. Alternatively, an explanation of why a DMC is not needed	
4	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
5	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
6	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
7	Ethics and dissemination			
8	Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	Page 16/17
9	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
10	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
11	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
12	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
13	Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 16/17

1	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
2	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
3	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
4	Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
5	Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
6	Appendices			
7	Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Available upon request
8	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
9	None The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons Attribution License CC-BY-NC. This checklist can be completed online using https://www.goodreports.org/ , a tool made by the EQUATOR Network in collaboration with Penelope.ai			
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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:	<i>BMJ Open</i>
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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

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Manuscripts

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3 **Study protocol for a randomized, double-blind, placebo-controlled crossover trial**
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5 **assessing the impact of the SGLT2 inhibitor empagliflozin on postprandial hypoglycaemia**
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7 **after gastric bypass**
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10 THE DEEP-EMPA TRIAL
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14 Antonio Ferreira¹, Ahmed Fahiem Abdelsalam Emara¹, David Herzog¹, Andreas Melmer¹,
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Abstract

Introduction:

Postprandial hypoglycaemia after gastric bypass surgery (also known as postbariatric hypoglycaemia or PBH) is an increasingly encountered clinical problem. 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 $< 3.0\text{ mmol/L}$). 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 \pm 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

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2
3 analogues, diazoxide and/or calcium channel blockers. The use of these medications is limited
4 by poor tolerability, inconvenient mode of administration, high costs or restricted availability
5 (e.g. acarbose no longer available on the Swiss market) [8, 16].
6
7

8 In a proof-of-concept study, a single dose of 10 mg empagliflozin was administered to 12
9 patients with postbariatric hypoglycaemia and significantly lowered the proportion of patients
10 experiencing hypoglycaemia during a standardised mixed meal tolerance test compared to
11 placebo (2 vs. 7 translating into a 74% risk reduction) [17]. Empagliflozin is an inhibitor of the
12 sodium-glucose cotransporter 2 (SGLT2) [18] that resides in the brush border membrane of
13 proximal tubular cells in the kidney and reabsorbs ~90 % of glucose filtered at the glomerulus
14 [19]. Empagliflozin blocks the physiological glucose reabsorption in the proximal tubule from
15 the glomerular filtrate, thereby reducing postprandial hyperglycaemia through increased
16 urinary glucose excretion. A dose-dependent increase in urinary glucose excretion and
17 reduction of plasma glycaemic exposure was observed [20, 21]. Inhibition of SGLT2 with
18 empagliflozin and other SGLT2 inhibitors were also shown to stimulate endogenous glucose
19 production, which was accompanied by an increase in plasma glucagon levels [22-24].
20
21 Empagliflozin 10 mg or 25 mg once daily is approved for the treatment of type 2 diabetes and
22 was also shown to exert cardiovascular and renal protection, independent of its glucose-
23 lowering effect [20, 25, 26].
24

25 As far as safety is concerned, therapy with SGLT2 inhibitors is generally well tolerated. An
26 increased incidence of genital infections and (although rare) euglycaemic ketoacidosis are
27 known side effects. The latter is mainly observed in patients with type 1 diabetes and less
28 frequently in those with type 2 diabetes [18]. No cases of euglycaemic ketoacidosis in
29 individuals without diabetes treated with SGLT2 inhibitors have been reported.
30
31

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 placebo 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].
 - o 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
 - o 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
 - o 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

1
2 first 3 days of data of each period will be discarded.
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5 The following variables will be assessed to address the effect on glucose variability:
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- 8 - Mean coefficient of variability based on sensor glucose
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10 ○ The outcome will be calculated from day 1 to day 20 of intake of IMP/placebo
11 (i.e. aggregated measures of the outcome will be calculated for each period). The
12 first 3 days of data of each period will be discarded.
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15 The following variables will be assessed to address the effect on hypoglycaemia:
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- 21 - Proportion of participants experiencing hypoglycaemia (defined as plasma
22 glucose<3.0mmol/L) during the mixed meal tolerance test.
23
24 ○ The outcome will be assessed during the mixed meal test on the day of the
25 experimental visit at the end of each study period (day 20-24 of the respective
26 study period).
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28 - Nadir plasma glucose during the mixed meal test
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30 ○ The outcome will be assessed during the mixed meal test on the day of the
31 experimental visit at the end of each study period (day 20-24 of the respective
32 study period).
33
34 - Percent time spent with sensor glucose <3.0mmol/L
35
36 ○ The outcome will be calculated from day 1 to day 20 of intake of IMP/placebo
37 (i.e. aggregated measures of the outcome will be calculated for each period). The
38 first 3 days of data of each period will be discarded.
39
40 - Percent time spent with sensor glucose <2.8mmol/L (in accordance with a recently
41 published International consensus on the diagnosis of postbariatric hypoglycaemia) [28].
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43 ○ The outcome will be calculated from day 1 to day 20 of intake of IMP/placebo
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(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
 - o 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)
 - o 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.
 - o 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
 - o 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)
 - o 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 $\geq 30\text{g}/24\text{h}$ and $<30\text{g}/24\text{h}$) 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 \geq 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

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2 participation will be reimbursed for their efforts and time (CHF 300 plus study-related travel
3 costs).
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10 Exclusion criteria:
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- 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

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43 **Randomization**
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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.

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58 **Study procedures**
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3 Eligible individuals will be randomized in equal proportions to 20 days 25 mg empagliflozin
4 followed by 20 days of placebo or vice-versa, taken once daily per os in the morning. Placebo
5 will be administered in a form identical to empagliflozin. Before randomization, participants
6 will attend a baseline visit (see Figure 1). Participants will remain on the assigned IMP/placebo
7 for 20 ± 4 days. During day 19 of the IMP intake period, participants will perform a 24h urine
8 collection. Instructions for the urine collection will be given at the time of the baseline visit and
9 participants will be reminded by an email or phone call immediately prior to the collection
10 period. On day 20, participants will attend the clinical research facility to undergo a
11 standardised mixed meal tolerance consisting of a breakfast roll with butter and jam, combined
12 with a fruit yogurt (500kcal, 74g of carbohydrates, 18g of fat and 12g of protein). Participants
13 will be asked to ingest the meal within 15 minutes in an upright position. Frequent blood
14 sampling for plasma glucose (Accu-Chek Inform II, Roche Diagnostics), insulin, C-peptide and
15 glucagon (immunometric assays by Roche, Siemens and Mercodia) at baseline and 10 min, 20
16 min, 30 min, 60 min, 90 min, 120 min, 135min, 150min following mixed meal ingestion will
17 be performed. Additionally, ketone levels (3-beta-hydroxybutyrate) will be assessed at baseline
18 and 30 min, 60 min following mixed meal ingestion using a point-of-care device (FreeStyle
19 Precision Neo, Abbott) to inform about potential effects of empagliflozin on fasting ketogenesis
20 due to the known shift to fatty substrate utilization as well as the extent of the suppressive effect
21 of postprandial insulin [32]. The two study periods will be separated by a wash out period of
22 2-6 weeks. During the two 20 days periods, participants will be fitted with a blinded continuous
23 glucose monitor (Dexcom G6) and record symptoms and carbohydrate intake (semiquantitative,
24 e.g. ≥ 30 vs. < 30 g, according to nutritional guidelines for the management of postbariatric
25 hypoglycaemia [15]) in an electronic diary. The same diary will be also used to monitor
26 adherence to IMP/placebo. Two weeks after completion of the second treatment, participants
27 will receive a phone call to inquire about a general well-being and safety events.
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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

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3 primary and secondary outcomes will be accompanied by p-values and hypothesis testing with
4 a significance level of 0.05 using two-sided tests.
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8 The main analyses will be done based on an intention-to-treat (ITT) basis, whereby all
9 randomized participants will be analysed in the allocated group regardless of any protocol
10 violations such as cross-overs (which can only happen accidentally in this trial), subjects that did
11 not receive the treatment in the randomised sequence or subjects that did not comply with the
12 intervention. A sensitivity analysis, done based on the per-protocol (PP) basis, will be
13 performed including only participants compliant to the IMP intake. Non-compliance is defined
14 as: in any of the two treatment periods, 1) more than two non-consecutive days with missed
15 intake of the allocated capsule; or 2) more than four missed tablets (i.e. to be compliant, patients
16 must take at least 16 tablets); or 3) missed intake on day of visit 1 or 2.
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33 Primary Analysis

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35 Linear mixed effects model will be used for the statistical analysis. The mixed effects model
36 will contain the treatment and period as fixed effects to adjust for any period effects, and a
37 random effect for participants to account for within-participant correlation of repeated
38 measurements. Residual values will be assessed for normality using the Shapiro-Wilk test.
39 Transformations to normality for variables not fulfilling normality assumptions will be
40 considered (e.g. log, Box-Cox etc.). All primary and secondary endpoints will be analysed using
41 this approach. We will notably not formally test for possible carry-over effects due to the long
42 wash out period and to avoid any inflation of type I error. Mean \pm SD or summary statistics
43 appropriate to the variable type will be reported for the primary and secondary efficacy
44 outcomes for the two treatments. Results from statistical analyses will be presented as paired-
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3 differences \pm SD along with 95 % confidences intervals. A two-sided p-value will be reported
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5 and a p-value <0.05 will be considered statistically significant.
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11 **Statistical interim analysis**
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17 No interim analysis is planned.
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20 **Safety analysis**
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24 A descriptive summary of safety events will be tabulated for each treatment. No formal
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26 statistical testing will be applied. Safety outcomes entail the following
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38 - Serious Adverse Events
39 - Adverse Events of Special Interest
40 - Vital signs
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55 **Quality assurance and control**
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58 **Monitoring**
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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).

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55 **Data management**
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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

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3 be exported in a CSV format and transferred to the statistical software package for analysis. All
4 data will be archived and secured in the database for at least 10 years.
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10 **Patient and public involvement**

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

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

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54 **Ethics and dissemination**

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56 The DEEP-Empa trial will be performed in accordance with the protocol and with principles
57 enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical
58 Practice and the International Conference on Harmonization of Technical Requirements for
59 Pharmaceuticals for Human Use. The trial will be registered in the ClinicalTrials.gov database.
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3 Practice issues by the International Council for Harmonisation of Technical Requirements for
4 Pharmaceuticals for Human Use (ICH), the Swiss Law and Swiss regulatory authorities'
5 requirements. The Ethics Committee Bern and Swissmedic will receive annual reports and will
6 be notified of safety events or measures, as well as protocol amendments or change in study
7 status (start/stop). The study was approved by the Ethics Committee Bern in September 2021,
8 and by Swissmedic in November 2021. Registration was issued at ClinicalTrials.gov
9 (NCT05057819). Patient recruitment started in December 2021 and at the time of submission,
10 five participants have been enrolled. Study completion is anticipated in December 2022, and
11 first results are expected in Q1 of 2023. No publications containing results of this study have
12 already been published or submitted to any journal.
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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.

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1
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3 The study is fully supported by the Swiss National Science Foundation (PCEGP3_186978/1).
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6 The trial will also receive intramural support of the Bern University Hospital for local laboratory
7 analyses.
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11 ***Author's contributions***
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13 LB is the Sponsor-investigator of the trial and procured funding. LB and DH conceived the
14 study. LB, DH and AM wrote the study protocol and registered the study. AFacc. and CDM
15 were involved in development of the methodology and data analysis plan. LB, DH and CTN
16 wrote the statistical analysis plan. LB, DH and AF coordinate the study. LB and AF are involved
17 in the recruitment of patients and patient care. AV is involved in patient care. LB, AF, AE
18 drafted the first protocol manuscript. All authors contributed to the manuscript and all authors
19 read and approved the final version.
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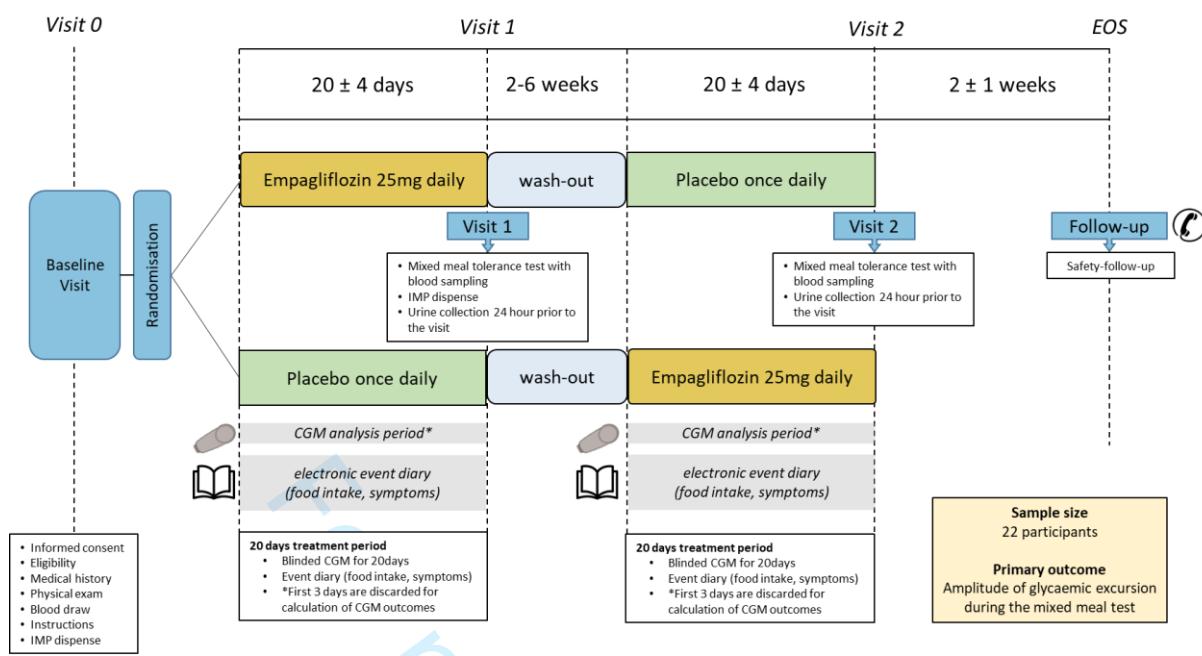
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Figures

50 **Figure 1.** The Deep Empa Trial study design. CGM, continuous glucose monitoring; IMP, 51 investigational medicinal product; EOS, end of study visit.
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HÔPITAL UNIVERSITAIRE DE BERNEUniversitätsklinik für Diabetologie,
Endokrinologie, Ernährungsmedizin
und Metabolismus

1 1
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3 3 Anfrage zur Teilnahme an medizinischer Forschung:
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Wirkung von Empagliflozin auf Unterzuckerungen nach Magenbypass-Operation – eine randomisiert-kontrollierte Doppelblind-Studie

10 Sehr geehrte Dame, sehr geehrter Herr

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

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

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

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5 41 Betreuungspersonal wissen, ob Sie Medikament oder Placebo einnehmen
6 42 (sogenannt doppelte Verblindung).
7 43 • Zu Beginn überprüfen wir Ihre Eignung zur Studienteilnahme, informieren Sie über
8 44 den Studienablauf und holen Ihre schriftliche Einwilligung ein. Sie erhalten dann die
9 45 erste Dose des Medikaments (Empagliflozin oder Placebo).
10 46 • Nach 20 Tagen werden Sie bei uns ein Frühstück einnehmen. Wir werden davor
11 47 und danach Blut zur Messung des Blutzuckers und von Hormonen entnehmen.
12 48 Dieser Besuch dauert ca. 3 Stunden.
13 49 • Nach einer Pause von 2-6 Wochen erhalten Sie das zweite Medikament. Nach
14 50 wiederum 20 Tagen führen wir denselben Test mit Frühstück und regelmässigen
15 51 Blutentnahmen bei Ihnen durch (Dauer wiederum ca. 3 Stunden)
16 52 • Während der Einnahme des Medikaments wird Ihr Zuckerverlauf mit einem Gerät,
17 53 welches auf der Haut getragen wird, aufgezeichnet. Den Zeitpunkt der Mahlzeiten,
18 54 welche Sie zu sich nehmen und allfällige Beschwerden dokumentieren Sie
19 55 elektronisch.

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24 56 **Welcher Nutzen und welches Risiko sind damit verbunden?**

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26 57 **Nutzen**

- 27
28 58 • Sie tragen mit Ihrer Teilnahme zur Verfügbarkeit neuer Behandlungsmöglichkeiten
29 59 von Unterzuckerung nach Magenbypass-Operationen bei.
30 60 • Durch ihre Teilnahme helfen Sie künftigen Patientinnen und Patienten.

31
32 61 **Risiko und Belastung**

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34 62 • Empagliflozin ist zugelassen zur Behandlung von Diabetes und hat ein sehr
35 63 günstiges Verträglichkeitsprofil.
36 64 • Bei Menschen mit Diabetes sind die häufigsten Nebenwirkungen vermehrtes
37 65 Wasserlassen und Harnwegsinfekte.

38
39 66 Mit Ihrer Unterschrift am Ende des Dokuments bestätigen Sie, dass Sie freiwillig an der Studie
40 67 teilnehmen und, dass Sie die Inhalte des gesamten Dokuments verstanden haben.
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45 70 **Detaillierte Informationen**

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7 72 **1. Ziel und Auswahl**8 73 Unser Forschungsprojekt bezeichnen wir in diesem Informationsschreiben als *Studie*. Wenn Sie an
9 74 dieser Studie teilnehmen, sind Sie eine *Studienteilnehmerin* bzw. ein *Studienteilnehmer*.

10 75

11 76 Bevor ein Medikament bei einer Erkrankung angewendet wird, muss es bei Studienteilnehmern
12 77 wissenschaftlich untersucht werden. Das Ziel dieser Studie ist es, den Nutzen einer neuen
13 78 Behandlung bei Menschen, welche an Unterzuckerungen nach dem Essen (sog. „postprandialen
14 79 Hypoglykämien“) als Folge einer Magenbypass-Operation leiden, zu untersuchen.15 80 Bei dem Medikament handelt es sich um das Medikament Jardiance® (Wirkstoff: Empagliflozin), das
16 81 in der Schweiz aktuell für die Behandlung von Patient*Innen mit Zuckerkrankheit (Diabetes)
17 82 zugelassen ist. Daten aus einer kürzlich veröffentlichten Studie von Forschenden der Universität
18 83 Basel legen nahe, dass die Einnahme von Empagliflozin im täglichen Leben von Patient*Innen nach
19 84 Magenbypass-Operation Blutzuckerschwankungen und das Auftreten von Unterzuckerungen nach
20 85 Mahlzeiten verringern kann. Empagliflozin hemmt die Zuckerwiederaufnahme in der Niere und
21 86 verringert so den Blutzuckeranstieg nach der Einnahme zuckerhaltiger Speisen. Durch den
22 87 geringeren Blutzuckeranstieg wird weniger Insulin (Blutzucker-senkendes Hormon) ausgeschüttet,
23 88 womit das Risiko für Unterzuckerungen und Blutzuckerschwankungen kleiner wird. In der Studie
24 89 verwenden wir die bei Diabetes-Patient*Innen zugelassene Dosis von 25 mg pro Tag. Bei gesunden
25 90 Personen wurden Dosen bis zu 800 mg pro Tag getestet ohne dass Sicherheitsprobleme auftraten.

26 91

27 92 Wir fragen Sie an, da Sie an Unterzuckerungen nach dem Essen leiden, vor mehr als einem Jahr
28 93 eine Magenbypass-Operation erhielten und Älter als 18 Jahre sind. Von der Teilnahme
29 94 ausgeschlossen sind Personen, die nicht für die Einnahme von Empagliflozin (nach Ermessen
30 95 des/der Prüfarztes/Prüfärztin) geeignet sind. Weitere Ausschlusskriterien sind komplizierte
31 96 Harnwegsinfekte, Einschränkungen der Nierenfunktion, aktuelle oder geplante Schwangerschaft,
32 97 Stillen oder die Einnahme von Medikamenten, die den Blutzucker während der Studienzeit
33 98 beeinflussen.

34 99

35 100 **2. Allgemeine Informationen**

- 36 101 ▪ Dieses Projekt wird mit insgesamt 22 Erwachsenen am Inselspital Bern durchgeführt.
37 102 Es wird nach dem Zufallsprinzip entschieden (sogenannte Randomisierung), ob Sie zuerst mit
38 103 Empagliflozin 25 mg oder Placebo (gleich aussehende Tablette ohne Wirkstoff) behandelt
39 104 werden, oder umgekehrt. Alle Teilnehmer*Innen werden beiden Behandlungen unterzogen: eine
40 105 Hälfte wird mit Empagliflozin starten, und danach Placebo erhalten, die andere Hälfte wird in
41 106 umgekehrter Reihenfolge behandelt. Weder Sie noch Ihr medizinisches Betreuungsteam
42 107 erfahren die Gruppenzuteilung (sogenannt doppelte Verblindung). Nur durch die Placebo-
43 108 Kontrolle kann festgestellt werden, ob es Unterschiede zwischen dem spontanen Verlauf und
44 109 der Behandlung mit Empagliflozin gibt. Beide Tabletten (Empagliflozin und Placebo) werden
45 110 während jeweils 20 Tagen, mit einer Pause von 2-6 Wochen, einmal täglich eingenommen.
- 46 111 ▪ Das Ansprechen auf die Therapie wird mit einem Mahlzeitentest an unserer Klinik am Tag 20
47 112 jeder Behandlungsphase untersucht. Dabei erhalten Sie ein Frühstück. Davor und danach
48 113 werden regelmässige Blutentnahmen durchgeführt. Während jeder Behandlungsphase werden
49 114 Sie ausserdem ein Messgerät zur fortlaufenden Messung des Zuckers (sogenanntes
50 115 „kontinuierliches Glukosemessgerät“) auf der Haut tragen und die Einnahme von Mahlzeiten und
51 116 allfällige Beschwerden elektronisch festhalten. Am Tag 19 jeder Behandlungsphase müssen Sie
52 117 zudem eine 24-Stunden-Urinsammlung durchführen.
- 53 118 ▪ Empagliflozin ist in der Schweiz zur Behandlung von Diabetes zugelassen. Aufgrund seiner
54 119 Wirkungsweise wird vermutet, dass Empagliflozin auch bei Unterzuckerung nach Einnahme von
55 120 Mahlzeiten nach z.B. einer Magenbypass-Operation wirken kann. Empagliflozin hat auch bei
56 121 Menschen ohne Diabetes ein gutes Sicherheitsprofil.

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5 122 ▪ Die Studie wird so durchgeführt werden, wie es die Gesetze in der Schweiz vorschreiben.
6 123 Ausserdem beachten wir alle international anerkannten Richtlinien. Die zuständige kantonale
7 124 Ethikkommission und Swissmedic haben die Studie geprüft und bewilligt. Eine Beschreibung
8 125 dieser Studie finden Sie auch auf der Internetseite des Bundesamtes für Gesundheit:
9 126 www.kofam.ch.

10
11 127 **3. Ablauf**

12 128 Der Ablauf zur Teilnahme an der Studie ist in Abbildung 1 dargestellt.

13 129 Bei Ihrem ersten Besuch (Visite 0) prüfen wir Ihre Studieneignung, klären allfällige Fragen und holen
14 130 - sofern Sie an der vorliegenden Studie teilnehmen möchten - Ihr schriftliches Einverständnis ein.
15 131 Wenn Sie Medikamente einnehmen, die den Blutzucker beeinflussen aber an der Studie teilnehmen
16 132 wollen, werden diese Medikamente für eine gewisse Zeit gestoppt. Dies erklärt Ihnen Ihr Prüfarzt/
17 133 Ihre Prüfärztin. Wir werden Ihnen die erste Flasche mit Medikament (entweder Empagliflozin oder
18 134 Placebo) aushändigen und erklären Ihnen das Tragen des kontinuierlichen Glukosemessgeräts, wie
19 135 Sie Mahlzeiten und Beschwerden elektronisch festhalten und die 24 Stunden-Urinsammlung vor
20 136 dem zweiten Besuch (Visite 1).

21 137 Sie nehmen nun jeden Tag eine Tablette des Medikaments am Morgen ein. Am 19. Tag werden Sie
22 138 beginnen, Ihren Urin für 24 Stunden zu sammeln. Am 20. Tag der Einnahme erscheinen Sie in
23 139 nüchternem Zustand zur Visite 1 an unserer Klinik. Sie werden bei uns ein Frühstück einnehmen.
24 140 Wir werden davor und danach Blut entnehmen um den Zucker im Blut und Hormone zu messen,
25 141 welche Einfluss auf den Blutzucker haben. Pro Test werden wir 75 ml Blutentnahmen, was für Ihre
26 142 Gesundheit unproblematisch ist (Vergleich: bei einer Blutspende werden 450-500ml Blut
27 143 entnommen). Der Test dauert ca. 3 Stunden. Im Sammelurin, welchen Sie zur Visite mitbringen,
28 144 messen wir die Zuckerausscheidung über die Niere. Die kontinuierliche Glukosemessung und das
29 145 Erfassen der Mahlzeiten und Beschwerden dienen der Auswertung der Blutzuckerschwankungen
30 146 und Beschwerden während der Einnahme des Medikaments. Am Schluss der Visite 1 erhalten Sie
31 147 die 2. Flasche mit Medikament (entweder Empagliflozin oder Placebo). Nach einer Pause von 2-6
32 148 Wochen nehmen Sie erneut für täglich eine Tablette des Medikaments am Morgen für 20 Tage ein.
33 149 Am Tag 20 erscheinen Sie zur Visite 2 an unserer Klinik. Die kontinuierliche Glukosemessung, das
34 150 Festhalten von Mahlzeiten und Beschwerden sowie die Urinsammlung am Tag 19 der
35 151 Tabletteneinnahme führen Sie unverändert durch. Der Ablauf von Visite 2 ist genau gleich wie jener
36 152 von Visite 1.

37 153 Nach Visite 2 endet die Behandlung der Studie. Nach 2 Wochen werden Sie telefonisch zu Ihrem
38 154 Gesundheitszustand befragt.

39 155
40 156 Es kann sein, dass wir Sie von der Studie vorzeitig ausschliessen müssen. Das kann deshalb
41 157 geschehen, wenn bei Ihnen Umstände auftreten, welche die weitere Teilnahme an der Studie
42 158 verbieten, oder der Prüfarzt/die Prüfärztin der Meinung ist, dass eine weitere Teilnahme an der
43 159 Studie Ihre Gesundheit gefährdet. In diesem Fall werden Sie zu Ihrer Sicherheit nach 2 Wochen
44 160 kontaktiert und gegebenenfalls an unserer Klinik untersucht. Bitte bringen Sie dann alle
45 161 Medikamente und Materialien, welche wir Ihnen gegeben haben, zu uns zurück. Ihr Hausarzt/Ihre
46 162 Hausärztin wird über die Studienteilnahme informiert werden.

47 163
48 164 **4. Nutzen**

49 165 Durch diese Studie werden wir wichtige Erkenntnisse zu neuen Behandlungsmöglichkeiten von
50 166 postprandialen Hypoglykämien nach Magenbypass-Operation gewinnen. Diese sind von Nutzen für
51 167 andere Personen, die dieselben Beschwerden haben.

52 168
53 169 **5. Freiwilligkeit und Pflichten**

54 170 Eine Teilnahme ist freiwillig. Wenn Sie nicht an dieser Studie teilnehmen oder später Ihre Teilnahme
55 171 zurückziehen wollen, müssen Sie dies nicht begründen. Ihre medizinische Behandlung/Betreuung
56 172 ist unabhängig von Ihrem Entscheid gewährleistet.

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5 173 Wenn Sie an der Studie teilnehmen, müssen Sie bestimmte Regeln beachten. Dies ist notwendig
6 174 für Ihre Sicherheit und Gesundheit. Wir werden Sie dabei bestmöglich unterstützen. Als
7 175 Studentteilnehmende/r sind Sie verpflichtet,
8 176
9 177 ▪ den medizinischen Anweisungen Ihres/Ihrer Prüfarztes/Prüfärztin zu folgen und sich an den
10 178 Studienplan zu halten,
11 179 ▪ in nüchternem Zustand zu den Visiten 1 und 2 zu erscheinen (das heisst, dass Sie ab Mitternacht
12 180 nichts mehr essen und bei Bedarf nur mehr Wasser trinken). Das Medikament können Sie auch
13 181 an den Tagen von Visite 1 und 2 jeweils am Morgen mit einem Schluck Wasser einnehmen. Das
14 182 gilt auch für Ihre allfälligen weiteren Medikamente.
15 183 ▪ bei Visite 1 und 2 die Flasche mit Medikament mitzubringen.
16 184 ▪ Ihren Prüfarzt/Ihre Prüfärztin über Änderungen Ihres Gesundheitszustandes zu informieren.
17 185 Melden Sie insbesondere auch neue Symptome, neue Beschwerden und Änderungen in Ihrem
18 186 Befinden (auch nach Studienende/-abbruch, z.B. bis die unerwünschte Wirkung abklingt);
19 187 ▪ gleichzeitige Behandlungen und Therapien, denen sie sich während der Teilnahme an der Studie
20 188 bei einem anderen Arzt/einer anderen Ärztin unterziehen möchten, erst mit Ihrem Prüfarzt/Ihrer
21 189 Prüfärztin zu besprechen, und
22 190 ▪ Ihren Prüfarzt/Ihre Prüfärztin immer über die Einnahme von zusätzlichen Medikamenten zu
23 191 informieren. Nennen Sie bitte alle Medikamente, auch solche, die Sie selbst gekauft haben, für
24 192 die Sie kein Rezept brauchen oder alternativmedizinische Präparate.
25 193

26 194 **6. Risiken und Belastungen**

27 195 Empagliflozin hat sich während der letzten Jahre als ein Medikament mit sehr guter Verträglichkeit
28 196 erwiesen. Bei Menschen ohne Diabetes wurden hohe Dosen bis zu 800 mg pro Tag getestet, mit
29 197 guter Verträglichkeit.

30 198 Folgende unerwünschte Wirkungen von Empagliflozin werden bei Personen mit Diabetes oft
31 199 beobachtet:

- 32 200 ▪ Harnwegsinfektionen, insbesondere Pilzinfektionen. Diese sind in der Regel harmlos und
33 201 lassen sich gut behandeln.
34 202 ▪ Bei Diabetes-Patienten mit fehlender oder verringriger eigener Insulinproduktion liegt ein
35 203 erhöhtes Risiko für die Ketoazidose vor. Ketoazidose bedeutet, dass sich saure Stoffe im
36 204 Blut ansammeln. Bei Personen ohne Diabetes sind keine Fälle von Ketoazidose in
37 205 Zusammenhang mit Empagliflozin bekannt. Bei Personen mit Unterzuckerungen nach
38 206 Magenbypass-Operation ohne Diabetes ist eine Ketoazidose sehr unwahrscheinlich.
39 207 ▪ Bei gleichzeitiger Einnahme von anderen Diabetes-Medikamenten (Ausschlusskriterium für
40 208 Studienteilnahme), die selbst zu Unterzuckerungen führen können (v.a. Insulin), ist das
41 209 Risiko für Unterzuckerungen erhöht.
42 210

43 211 Unabhängig von der Einnahme des Medikaments bestehen folgende weiteren Risiken:

- 44 212 ▪ Das Tragen des kontinuierlichen Glukosemessgeräts kann zu Hautreizungen führen.
45 213 ▪ Die Einlage der Venenverweilkäne für die Blutentnahmen an Visite 1 und 2 kann zu
46 214 Blutergüssen und sehr selten zu Venenentzündungen führen.
47 215 ▪ Das kontinuierliche Glukosemessgerät muss im Falle bestimmter Untersuchungen (vor allem
48 216 bildgebender Verfahren) entfernt werden. Bitte informieren Sie Ihren Prüfarzt/ Ihre Prüfärztin,
49 217 wenn bei Ihnen während der Studienzeit eine bildgebende Untersuchung geplant wird.
50 218

51 219 **Für Frauen, die schwanger werden können**

52 220 Es liegen nur sehr begrenzte Erfahrungen über die Anwendung von Empagliflozin bei schwangeren
53 221 Frauen vor. Studien an Tieren ergaben keine Hinweise auf Schäden der Fruchtbarkeit oder der
54 222 Entwicklung des Nachwuchses im Mutterleib. Aufgrund möglicher Auswirkungen auf die Entwicklung
55 223 des Kindes beim Menschen ist die Anwendung von Empagliflozin während der Schwangerschaft zu
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5 225 vermeiden. Wir führen deswegen vor jeder Behandlungsphase bei Frauen im gebärfähigen Alter
6 226 einen Schwangerschaftstest im Urin durch. Frauen im gebärfähigen Alter müssen während der
7 227 gesamten Behandlung eine zuverlässige Verhütungsmethode anwenden (hormonelle Methode wie
8 228 Pille oder Spirale).

9 229 Sollten Sie während der Studie trotzdem schwanger werden, müssen Sie Ihren Prüfarzt/Ihre
10 230 Prüfärztin sofort informieren und dürfen nicht weiter an der Studie teilnehmen. In diesem Fall werden
11 231 Sie gebeten, Angaben über den Verlauf und den Ausgang der Schwangerschaft zu machen. Der
12 232 Prüfarzt/die Prüfärztin wird mit Ihnen das weitere Vorgehen besprechen.

13 233 Es gibt keine Informationen darüber, ob Empagliflozin beim Menschen in die Muttermilch übergeht.
14 234 Daten aus Studien an Tieren zeigten, dass Empagliflozin in die Milch übergeht und unerwünschte
15 235 Wirkungen auf die Entwicklung des Nachwuchses nach der Geburt hat. Ein Risiko für das
16 236 Neugeborene/Kind beim Menschen kann nicht ausgeschlossen werden. Das Stillen muss – wenn
17 237 eine Studienteilnahme dennoch erwünscht ist - während der Studienteilnahme unterbrochen
18 238 werden.

20 239 **7. Alternativen**

21 240 Die Teilnahme an der Studie ist mit Chancen und Risiken verbunden. Die Möglichkeiten zur
22 241 Behandlung postprandialer Hypoglykämien nach Magenbypass-Operation sind begrenzt und es gibt
23 242 keine zugelassenen Medikamente. Ernährungsumstellungen (v.a. das Vermeiden von Zucker in der
24 243 Nahrung) können sehr effektiv sein, sind aber nicht immer ausreichend und im Alltag oft schwer
25 244 umsetzbar. Der Wirkstoff „Acarbose“ hemmt die Zucker-Aufnahme im Dünndarm. Die Wirksamkeit
26 245 gegen postprandiale Hypoglykämien wurde in Studien nachgewiesen. Allerdings wird Acarbose oft
27 246 nicht vertragen (Blähungen, Bauchkrämpfe) und die Einnahme vor jeder Mahlzeit ist nicht
28 247 anwenderfreundlich. Acarbose ist zudem in der Schweiz nicht mehr erhältlich. Weitere Substanzen
29 248 sind sehr teuer, können ernste Nebenwirkungen haben und wurden bisher nur in Einzelfällen
30 249 eingesetzt. Ihr Prüfarzt/ Ihre Prüfärztin wird Sie im Gespräch darüber informieren.

31 250 **8. Ergebnisse**

32 251 Es gibt

- 33 252 1. Ergebnisse der Studie, die Sie direkt betreffen,
- 34 253 2. Ergebnisse der Studie, die zufällig entstehen (sogenannte Zufallsergebnisse)
- 35 254 3. End-Ergebnisse der gesamten Studie.

36 255 Zu 1: Ihr Prüfarzt/ Ihre Prüfärztin wird Sie im Verlauf der Studie über alle für Sie persönlich wichtigen,
37 256 neuen Ergebnisse und Erkenntnisse informieren. Sie werden mündlich und schriftlich informiert und
38 257 können dann erneut entscheiden, ob Sie an der Studie weiterhin teilnehmen möchten.

39 258 Zu 2: Zufallsbefunde sind sogenannte „Begleit-Ergebnisse“, also Ergebnisse, nach denen man nicht
40 259 gesucht hat, sondern die zufällig gefunden werden. Im Falle unserer Studie können dies Befunde
41 260 aus Blut- oder Urinsammlungen sein.

42 261 Bei Zufallsbefunden werden Sie informiert, wenn diese Befunde relevant für Ihre Gesundheit sind.
43 262 Das bedeutet, dass solche Befunde Ihnen dann mitgeteilt werden, wenn man zufällig eine bislang
44 263 nicht bekannte Erkrankung festgestellt hat oder eine noch nicht aufgetretene Erkrankung durch
45 264 Vorbeugung verhindern kann. Wenn Sie darüber nicht informiert werden wollen, sprechen Sie bitte
46 265 mit Ihrem Prüfarzt/ Ihrer Prüfärztin.

47 266 Zu 3: Ihr Prüfarzt/ Ihre Prüfärztin kann Ihnen am Ende der Studie eine Zusammenfassung der
48 267 Gesamtergebnisse zukommen lassen.

49 268 **9. Vertraulichkeit von Daten und Proben**

50 269 Im Rahmen der Studie werden persönliche und medizinische Daten erhoben. Nur wenige Fachleute
51 270 sehen Ihre unverschlüsselten Daten, und auch nur, um Aufgaben innerhalb der Studie zu erfüllen.

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.



UNIVERSITÄTSPITAL BERN

HÔPITAL UNIVERSITAIRE DE BERNE

Universitätsklinik für Diabetologie,
Endokrinologie, Ernährungsmedizin
und Metabolismus

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5 327 Sollten Sie durch die Teilnahme an dieser Studie einen Schaden erleiden, so wenden Sie sich bitte
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7 329 Versicherungs-Gesellschaft AG, Mythenquai 2, 8002 Zürich).
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13. Finanzierung

10 332 Die Studie wird durch den Schweizerischen National Fonds zur Förderung der wissenschaftlichen
11 333 Forschung finanziert. Das Medikament wird von Boehringer Ingelheim zur Verfügung gestellt.
12 334
13 335

14. Kontaktperson(en)

14 336 Sie dürfen jederzeit Fragen zur Studienteilnahme stellen. Auch bei Unsicherheiten oder Notfällen,
15 337 die während der Studie oder danach auftreten, wenden Sie sich bitte an:
16 338
17 339 Prof. Dr. med. et phil. Lia Bally (verantwortliche Ärztin/Prüferin)
18 340 Leiterin Forschung, Fachbereichsleiterin Ernährung und Metabolismus
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24 346 Während der Studie können Sie uns jederzeit unter den folgenden Telefonnummern erreichen:
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Kontakt für allgemeine Fragen

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Studieninformation DEEP-EMPA

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11	12	13	2021-01187
13	14	15	Titel der Studie (wissenschaftlich und Laiensprache):
14	15	16	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)
16	17	18	19
17	18	19	Wirkung von Empagliflozin auf Unterzuckerungen nach Magenbypass-Operation eine randomisiert-kontrollierte Doppelblind-Studie
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Universitätsklinik für Diabetologie,
Endokrinologie, Ernährungsmedizin
und Metabolismus

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5 421 **Einwilligungserklärung für Weiterverwendung von Daten und biologischem Material**
6 422 **in verschlüsselter Form**
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9 **BASEC-Nummer (nach Einreichung):**

2021-01187

10
11 **Titel der Studie**
12 **(wissenschaftlich und Laiensprache):**

13 Randomized, double-blind, placebo-controlled
14 crossover trial assessing the impact of the SGLT2
15 inhibitor empagliflozin on postprandial
16 hypoglycaemia after gastric bypass (the DEEP-
17 Empa trial)

18 Wirkung von Empagliflozin auf
19 Unterzuckerungen nach Magenbypass-
20 Operation eine randomisiert-kontrollierte
21 Doppelblind-Studie

22 **Teilnehmerin/Teilnehmer:**

23 Name und Vorname in Druckbuchstaben:

24 Geburtsdatum:

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26 424
27 425 Ich erlaube, dass meine verschlüsselten Daten und Proben aus dieser Studie für die medizinische
28 426 Forschung weiterverwendet werden dürfen. Die Proben werden in einer Biobank am Inselspital
29 427 Bern für zukünftige, noch nicht näher definierte Forschungsprojekte auf unbestimmte Zeitdauer
30 428 verwendet.

31 429
32 430 Ich habe verstanden, dass die Proben verschlüsselt sind und der Schüssel sicher aufbewahrt wird.
33 431 Die Daten und Proben können im In- und Ausland an andere Daten- und Biobanken zur Analyse
34 432 gesendet werden, wenn diese dieselben Standards wie in der Schweiz einhalten. Alle rechtlichen
35 433 Vorgaben zum Datenschutz werden eingehalten.

36 434
37 435 Ich entscheide freiwillig und kann diesen Entscheid zu jedem Zeitpunkt wieder zurücknehmen.
38 436 Wenn ich zurücktrete, bleiben die Daten und Proben verschlüsselt, da eine Anonymisierung im
39 437 vorliegenden Projekt nur mit einem unverhältnismäßig großen Aufwand an Zeit, Kosten und
40 438 Arbeitskraft möglich wäre. Ich informiere lediglich meine Prüfärztin/meinen Prüfarzt und muss
41 439 diesen Entscheid nicht begründen. Nach dem Wiederruf werden meine Daten und Proben für neue
42 440 Forschungsprojekte nicht mehr zur Verführung gestellt.

43 441
44 442 Normalerweise werden alle Daten und Proben gesamthaft ausgewertet und die Ergebnisse
45 443 zusammenfassend publiziert. Sollte sich ein für meine Gesundheit wichtiges Ergebnis ergeben, ist
46 444 es möglich, dass ich kontaktiert werde. Wenn ich das nicht wünsche, teile ich dies meiner
47 445 Prüfärztin/meinem Prüfarzt mit.

48 446
49 447 Wenn Ergebnisse aus den Daten und Proben kommerzialisiert werden, habe ich keinen Anspruch
50 448 auf Anteil an der kommerziellen Nutzung.

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Studieninformation DEEP-EMPA v2.1, 20.09.2021 Seite 11/13
Inselspital, Universitätsklinik für Diabetologie, Endokrinologie, Ernährungsmedizin und Metabolismus (UDEM), CH-3010
Bern



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Universitätsklinik für Diabetologie,
Endokrinologie, Ernährungsmedizin
und Metabolismus

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5 451 **Bestätigung der Prüfärztin/des Prüfarztes:** Hiermit bestätige ich, dass ich dieser
6 452 Teilnehmerin/diesem Teilnehmer Wesen, Bedeutung und Tragweite der Weiterverwendung von
7 453 Proben und/oder Daten erläutert habe.
8 454

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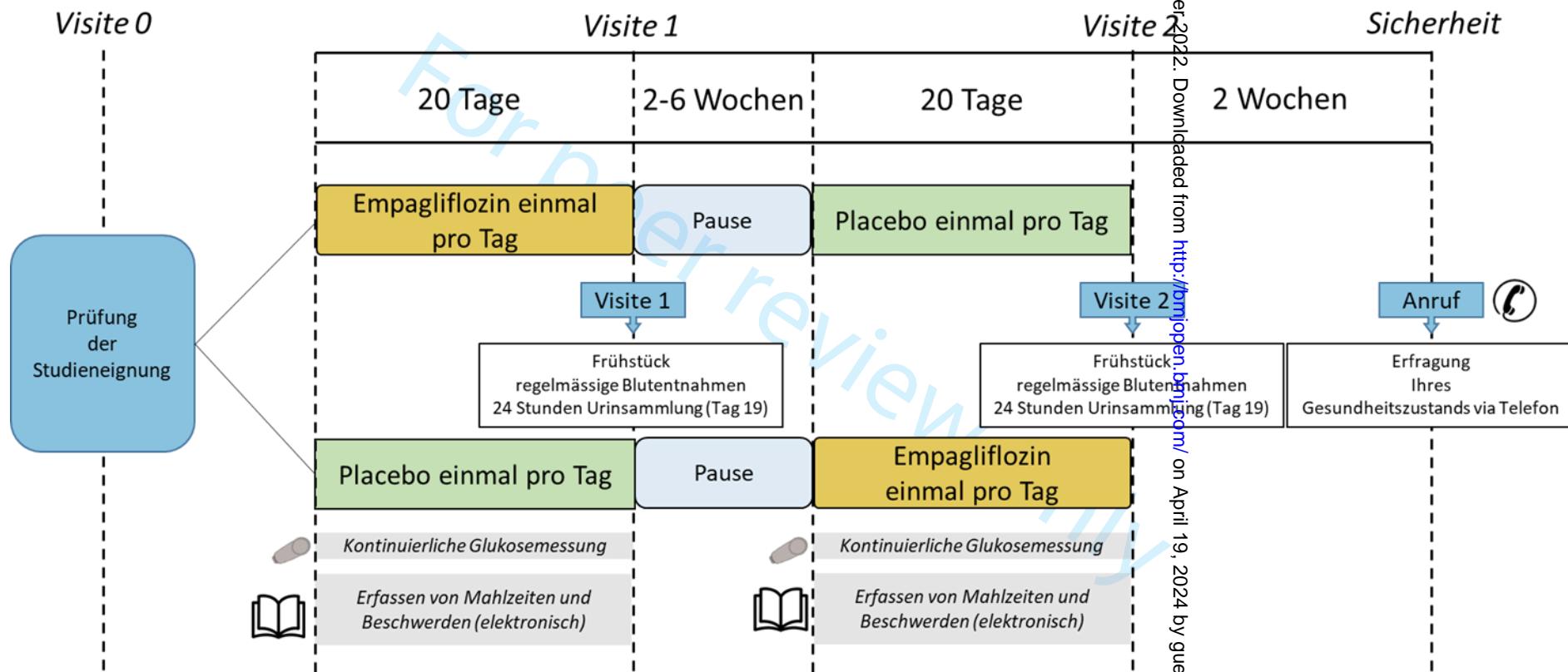
For peer review only

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458 **Abbildung 1: Studienablauf**

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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 SPIRIT reporting 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
Trial registration	#2a Trial identifier and registry name. If not yet registered, name of intended registry
Trial registration: data set	#2b All items from the World Health Organization Trial Registration Data Set
Protocol version	#3 Date and version identifier
Funding	#4 Sources and types of financial, material, and other support

1	Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	Page 17
2				
3	Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	Page 1
4				
5	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
6				
7	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
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33	Introduction			
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35	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
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42	Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	Page 4-6
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47	Objectives	#7	Specific objectives or hypotheses	Page 6
48				
49	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
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56	Methods:			
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58	Participants,			
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1
2 interventions, and
3 outcomes
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5 Study setting	6 #9	7 Description of study settings (eg, community clinic, 8 academic hospital) and list of countries where data 9 will be collected. Reference to where list of study 10 sites can be obtained	11 Page 9-12
11 Eligibility criteria	12 #10	13 Inclusion and exclusion criteria for participants. If 14 applicable, eligibility criteria for study centres and 15 individuals who will perform the interventions (eg, 16 surgeons, psychotherapists)	17 Page 10
18 Interventions: 19 description	20 #11a	21 Interventions for each group with sufficient detail to 22 allow replication, including how and when they will be 23 administered	24 Page 9
25 Interventions: 26 modifications	27 #11b	28 Criteria for discontinuing or modifying allocated 29 interventions for a given trial participant (eg, drug 30 dose change in response to harms, participant 31 request, or improving / worsening disease)	32 Page 9-12
33 Interventions: 34 adherence	35 #11c	36 Strategies to improve adherence to intervention 37 protocols, and any procedures for monitoring 38 adherence (eg, drug tablet return; laboratory tests)	39 Page 9-12
40 Interventions: 41 concomitant care	42 #11d	43 Relevant concomitant care and interventions that are 44 permitted or prohibited during the trial	45 Page 9-12
46 Outcomes	47 #12	48 Primary, secondary, and other outcomes, including 49 the specific measurement variable (eg, systolic blood 50 pressure), analysis metric (eg, change from baseline, 51 final value, time to event), method of aggregation (eg, 52 median, proportion), and time point for each 53 outcome. Explanation of the clinical relevance of 54 chosen efficacy and harm outcomes is strongly 55 recommended	56 Page 7-8
57 Participant timeline	58 #13	59 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	60 Page 9

1	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
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8	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 10
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12	Methods:			
13	Assignment of interventions (for controlled trials)			
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18	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
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30	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
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38	Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 17
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43	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 11
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48	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
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54	Methods: Data collection, management, and analysis			
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1	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
2				
3	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
4				
5	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
6				
7	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
8				
9	Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 12-15
10				
11	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
12				
13	Methods:			
14	Monitoring			
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16	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
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1	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
2	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
3	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
4	Ethics and dissemination			
5	Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	Page 16/17
6	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
7	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
8	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
9	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
10	Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 16/17

1	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
2	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
3	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
4	Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
5	Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
6	Appendices			
7	Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Available upon request
8	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
9	None The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons Attribution License CC-BY-NC. This checklist can be completed online using https://www.goodreports.org/ , a tool made by the EQUATOR Network in collaboration with Penelope.ai			
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