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

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ABSTRACT

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

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

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

STRENGTHS AND LIMITATIONS OF THIS STUDY

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

Trial registration number NCT05057819.

INTRODUCTION

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

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

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

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

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

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

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

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

METHODS AND DESIGN

Study objectives

Overall objective

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

Primary objective

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

Secondary objectives

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

Further objectives

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

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

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

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

Safety objectives

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

Study outcomes

Primary outcome

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

Secondary outcomes

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

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

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

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

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

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

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

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

Exploratory outcomes

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

Safety outcomes

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

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

Assessment of outcomes

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

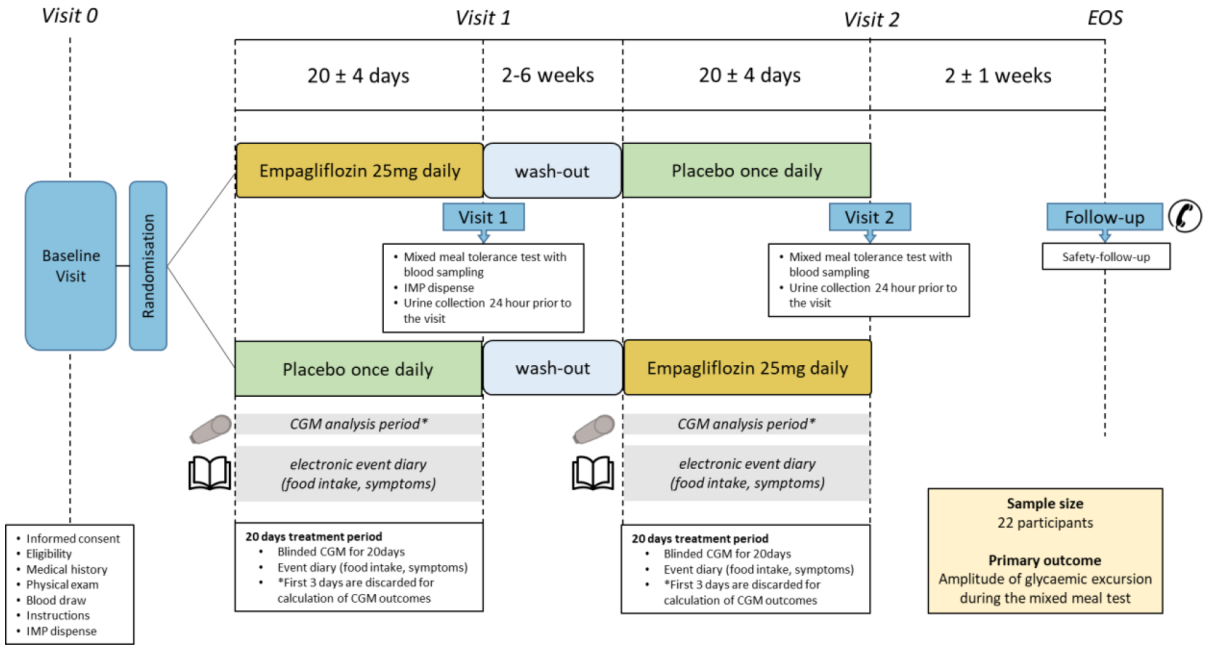

Figure 1 The DEEP-EMPA trial study design. CGM, continuous glucose monitoring; EOS, end of study visit; IMP, investigational medicinal product.

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

Study design

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

Study population

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

Exclusion criteria

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

Randomisation

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

Study procedures

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

Statistical methods

Sample size

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

Hypothesis

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

Statistical analysis

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

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

Primary analysis

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

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

Statistical interim analysis

No interim analysis is planned.

Safety analysis

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

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

Quality assurance and control

Monitoring

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

Data management

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

Patient and public involvement

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

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

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Competing interests None declared.

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

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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