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Canakinumab for the treatment of postprandial hypoglycaemia: study protocol for a randomised, placebo-controlled, parallel-group, double-blind, multicentric, superiority trial—the CanpHy study

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ABSTRACT

Introduction Postbariatric hypoglycaemia (PBH) is a complex medical condition with a significant impact on patients' quality of life. The underlying mechanisms remain to be elucidated. We have shown that food ingestion increases IL-1β and subsequently stimulates insulin secretion. We therefore hypothesised that overactivation of the IL-1β pathway could lead to PBH by promoting excessive insulin secretion after a meal. In a proof-of-concept study, we have shown that acute treatment with the IL-1 receptor antagonist anakinra can attenuate PBH after a single liquid mixed meal. This study aims to validate this therapeutic approach over a longer period of time using the long-acting anti-IL-1β antibody canakinumab.

Methods and analysis In this prospective, randomised, double-blind, placebo-controlled, multicentre trial, we plan to enrol 62 adult patients after bariatric surgery with frequent, postprandial hypoglycaemia (ie, <3.0 mmol/L and at least five hypoglycaemic episodes per week). Eligible subjects will be randomised to receive either single-dose 150 mg canakinumab (Ilaris, Novartis) subcutaneously (s.c.) or matched placebo (1.0 mL physiologic saline). For 28 days, patients are required to wear a blinded continuous glucose monitoring device (CGMS, Dexcom G6) and use a diary to track their hypoglycaemic episodes. Primary outcomes include health-related quality of life, measured by the SF-36, as well as postprandial hypoglycaemic events (glucose <3.0 mmol/L). A significant improvement in any one of these outcomes will be considered sufficient to demonstrate the clinical superiority of canakinumab over placebo. Secondary outcomes include patient-oriented measures such as postprandial hypoglycaemic symptoms, hypoglycaemia unawareness, fear of hypoglycaemia, as well as metabolic measures and safety assessments.

Ethics and dissemination The trial was approved by the Cantonal Ethics Committee 'Ethikkommission Nordwest- und Zentralschweiz' in January 2022 (#2021–02325), as well as by Swissmedic in April 2022 (#701280). Current, approved protocol version 1.3 of 28.03.2023. The study is actively recruiting. Results will be published in a relevant scientific journal and communicated to participants and relevant institutions through dissemination activities. Individual data are accessible on request.

Trial registration The study is registered with the www.clinicaltrials.gov registry (NCT05401578) and the Swiss National Clinical Trials Portal (SNCTP) on www.kofam.ch (SNCTP000004838).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ First study to evaluate the effect of long-term IL-1β antagonism in patients with frequent postbariatric hypoglycaemia by way of continuous glucose monitoring
⇒ Primary endpoints include both clinically relevant outcomes such as reduction in hypoglycaemic episodes and patient-reported quality of life in a real-world setting
⇒ Solid multicentric, placebo-controlled study design with a relatively large number of participants
⇒ SF-36 has not been verified for this specific group of patients and may have limited validity
⇒ Use of a patient diary to document hypoglycaemic episodes may introduce recall bias or inaccuracies in reporting symptoms

INTRODUCTION

Postbariatric hypoglycaemia (PBH) is a frequent medical condition, with 34%–56% of patients after sleeve gastrectomy and Roux-en-Y gastric bypass (RYGB)[1–4] affected. PBH decreases the quality of life (QoL)[5–7] and may also be responsible for secondary weight gain.[3] The rapid postprandial rise of plasma glucose is followed by an increased glucose-lowering reaction, mediated by insulin, insulinotropic incretins, polypeptides or other abnormal counter-regulatory mechanisms.[8–11] The exact mechanisms leading to hypoglycaemia are

unclear, and therapeutic options are warranted. Treatment of PBH consists of dietary intervention with carbohydrate control with five to six meals and reduced glycaemic index.[12 13] Medical, but off-label, therapeutic options comprise acarbose (α-glucosidase inhibitor), calcium channel blockers (diazoxide), somatostatin analogues (eg, octreotide, pasireotide).[12 14 15]

We propose that an exaggerated postprandial inflammatory response might contribute to PBH. Glucose has been shown to stimulate the production of Interleukin-1 beta (IL-1β).[16] Subsequent animal and human studies demonstrated that IL-1β plays a crucial role in the development of type 2 diabetes and its complications.[17] More recent research revealed that IL-1β is involved in the physiological regulation of insulin secretion.[18] After food intake, glucose and microbial products trigger an acute increase in myeloid cell-derived IL-1β, which supports postprandial insulin secretion.[19] This response may act as an initial defence mechanism against food- and gut-derived microbes. After gastric bypass surgery, food reaches the distal parts of the gastrointestinal tract much faster, causing an early glycaemic peak. We suggest that this leads to an excessive induction of IL-1β, resulting in an exaggerated insulin response, followed by hypoglycaemia. In a recent randomised, placebo-controlled, double-blind, crossover proof-of-concept study in patients with postprandial hypoglycaemia after RYGB, administration of IL-1 receptor antagonist anakinra (Kineret) lowered the risk of symptomatic hypoglycaemic episodes (requiring rescue glucose) by 26% in a standardised liquid mixed-meal-test setting via a significantly reduced secretion of insulin.[20] Clinical investigation in a larger patient population is warranted to replicate the findings on hypoglycaemia and directly evaluate clinical outcomes and patient-relevant benefits, with a focus on improving QoL. So far, there are no core outcome sets established for the treatment of PBH, and it is unclear which primary outcome would be most relevant to patients. To better understand the patient perspective and acceptable study settings, we collected information on patient preferences in an anonymous online survey. Patients with confirmed PBH preferred an improvement of their QoL (77%) over a reduction of hypoglycaemic episodes (25%).[7]

Canakinumab (Ilaris, Novartis) is a recombinant, human monoclonal IgG1/kappa antibody inhibiting IL-1β by neutralising its biological activity through binding to the IL-1 receptor. It has a strong affinity to and high specificity for IL-1 β.[21] Canakinumab has a peak serum concentration at 7 days after subcutaneous injection of 150 mg with a mean half-life time of 26 days. Its anti-inflammatory effect in diseases with chronic overactivation of the innate immune system led to approval by Swissmedic and the European Medicine Agency for the treatment of diseases such as cryopyrin-associated periodic syndrome (CAPS), familial Mediterranean fever (FMF) and Still's disease.[21 22] Recent data in patients with established cardiovascular disease showed that canakinumab reduces significantly the rate of cardiovascular events in a dose of 150 mg s.c. every 3 months.[23] Overall, more than 18 500 study participants received canakinumab. Canakinumab is associated with an increased incidence of serious infections, and isolated opportunistic or unusual infections have been reported.[22]

Canakinumab (Ilaris, Novartis) will be used in the recommended standard dose of 150 mg subcutaneously once.

We designed this randomised clinical trial to directly evaluate clinical outcomes and patient-relevant benefits of canakinumab treatment. We aim to determine whether canakinumab increases QoL and/or reduces the risk for hypoglycaemic episodes in patients with PBH.

STUDY OUTCOMES

Main objective

We designed this randomised clinical trial to directly evaluate clinical outcomes and patient-relevant benefits of canakinumab once at the beginning of a treatment period over 28 days in a real-world setting and to describe the efficacy and safety profile for this medical condition.

Primary outcomes

Treatment with canakinumab will be considered superior to placebo if it provides a directly patient-relevant benefit and improves health-related QoL (mental or functional aspects), or if a clinically relevant reduction in the number of hypoglycaemic episodes is shown at the end of the treatment phase (visit 5, day 29).

All three independent primary outcomes will be considered relevant for clinical decision-making. Demonstration of a relevant improvement in at least one of them is considered sufficient to guide clinical decisions and establish statistical superiority of canakinumab versus placebo.

- Quality of life (mental health; as assessed by the SF-36 mental health component score; MCS)
- Quality of life (physical health; as assessed by the SF-36 physical component score; PCS) Hypoglycaemic events are defined as glucose values below 3.0 mmol/L.

Secondary outcomes

Patient-oriented

- Postprandial symptoms of hypoglycaemia are defined as acute onset of typical symptoms according to Edinburgh Hypoglycaemia Scale along with a decreasing blood glucose level. The postprandial period is defined as 3 hours following meal intake.
- Hypoglycaemia unawareness (measured by modified Clarke score)
- Fear of hypoglycaemia (measured on a scale of 0 to 10)

Metabolism

- Time below range (TBR; % of sensor glucose readings and time between 3.0 and 3.8 mmol/L)
- Time in hypoglycaemia: % of sensor glucose readings and time below 3.0 mmol/L

- Pattern of sensor glucose, defined as the slope of postprandial increase (calculated as the maximal rate of increase observed over 20 min in the postprandial period) and decrease (calculated as the maximal rate of decrease over 20 min in the postprandial period)
- Glycaemic variability (defined as the coefficient of variation of sensor glucose)
- Mean amplitude of sensor glucose excursions
- Levels of fasting glucose, insulin, c-peptide, GLP-1, glucagon, free fatty acids, beta-hydroxybutyrate, HbA1c, IL-6, IL-1Ra and CRPBody weight

Harms

- Total adverse events
- Serious adverse events

All outcomes are measured 28 days after randomisation or refer to the period up to 28 days.

Adverse events and QoL will be assessed at 90 days as well.

Safety outcomes

Safety will be assessed by documentation of total and serious adverse events at every visit. Every adverse event will be reported by a study nurse or physician, and actions will be undertaken if necessary.

STUDY DESIGN

General study design and justification of design

This is a national, multicentre, 1:1 randomised, placebo-controlled, parallel-group, double-blind superiority trial and will investigate the effect of IL1 antagonism with canakinumab (150 mg s.c.) for 4 weeks on QoL and hypoglycaemic episodes in patients with frequent postprandial hypoglycaemia after bariatric surgery compared with placebo (Eligibility criteria section). The study consists of six visits as outlined in table 1 (study schedule) and figure 1 (study flow chart).

The study takes for each subject a maximum of 120 days (up to 30 days from screening to randomisation, 60 days until follow-up): with a screening date (visit 1, 1 hour; if necessary, a 10-day CGMS screening phase (Dexcom G6), randomisation/starting visit (visit 2, 1.5 hour) followed by a 28-day intervention period with two additional study days (visits 3 and 4, 0.5 hour, change of CGMS sensor, diary documentation, adverse events) and end of treatment visit (visit 5). A follow-up visit will be done 2 months after the end of the treatment phase (SF-36, adverse events).

Screening (visit 1, day -30 until -1, 1.0 h)

Patients will be recruited in outpatient clinics at the respective sites and informed about the scope of the study.

Table 1 Study schedule

Study period	Screening	Treatment/intervention period				Follow-up
Visit	1	2	3	4	5	6
Study day	Day −30 to day −1	1	Days 8–10	Days 18–20	Days 29–1 /+2 days	90±11 days
Patient information and written informed consent	x					
Demographics	x					
Medical History	x					
In-/exclusion criteria	x	x				
Physical examination including height	x					
Vital signs and weight	x	x			x	(x)
Laboratory tests	x	x			x	
Pregnancy test	x					
Randomisation		x				
Diary documentation	x		x	x	x	
CGMS documentation	x		x	x	x	
Administer study medication		x				
Administer CGMS sensor	x	x	x	x		
SF-36 questionnaire		x			x	x
Further questionnaires ► Modified Clarke score ► Fear of hypoglycaemia scale		x			x	x
Concomitant therapy	x	x	x	x	x	x
Adverse events		x	x	x	x	x

CGMS, continuous glucose monitoring system; SF-36, 36-item short form survey instrument.

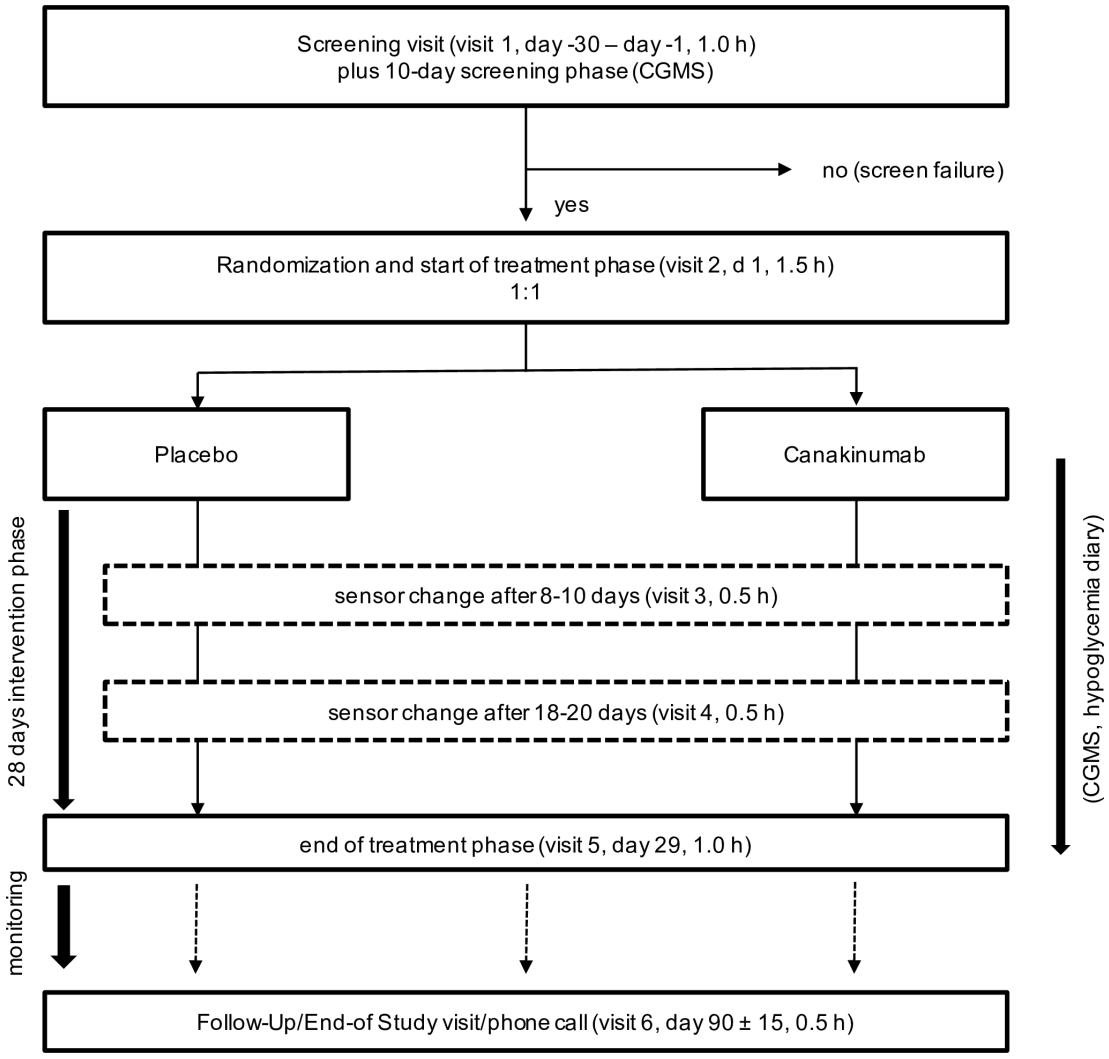

Figure 1 Study flow chart.

If patients agree to participate, the study physician will seek written informed consent and assess the frequency of postprandial hypoglycaemia, a complete medical history (time point and procedure of bariatric surgery, start of hypoglycaemic symptoms, diagnosis of postprandial hypoglycaemia, preoperative weight, nadir weight) and medication. A physical examination including anthropometric data (weight, height, BMI, blood pressure, heart rate, temperature) as well as blood laboratory analysis (blood smear, chemistry, HbA1c) will be done (Eligibility criteria section). If not already documented, otherwise, a 10-day screening phase using a blinded CGMS (Dexcom G6) is required to record hypoglycaemic episodes (glucose <3.0 mmol/L) and symptoms. Patients will be instructed in its use.

Randomisation

If patients fulfil all requirements for the study (Eligibility criteria section), they will be randomised at visit 2 to either placebo (1 mL 0.9% saline solution s.c.) or treatment with 1 mL 150 mg canakinumab solution s.c. in a 1:1 manner. Randomisation will be in blocks (sizes of four subjects) prepared by an independent staff member (simple sequential allocation randomisation schedule without stratifying factors). Unblinded study personnel at each site will allocate participants to a treatment group according to the site-specific randomisation list. Randomisation will be coordinated centrally to ensure uniform implementation across the sites.

Blinding procedures

Both subjects and investigators will be blinded. A nurse independent of the research group will be responsible for treatment blinding and preparation of trial drugs throughout the study.

Continuous glucose monitoring data will be reviewed by a third blinded party.

Unblinding

After all subjects have completed the study, the data will be unblinded to the investigators in order to complete the analysis of data. Dropouts will not be replaced. Unblinding of individual treatment assignment will occur when medically necessary on the principal investigator's request (emergencies with life-threatening symptoms

Table 2 Outline of laboratory analyses

	Screening visit	Study days 2 and 5
Material Analyses	EDTA (2.7 mL) differential blood count EDTA (2.7 mL) Glycated haemoglobin A1c (HbA1c) heparin (4.9 mL) ALAT, ASAT, total bilirubin, alkaline phosphatase, γ-glutamyl transpeptidase, creatinine, sodium, potassium, C-reactive peptide Pregnancy test (for women)	EDTA (2.7 mL) differential blood count EDTA (2.7 mL) Glycated haemoglobin A1c (HbA1c) heparin (4.9 mL) ALAT, ASAT, total bilirubin, alkaline phosphatase, γ-glutamyl transpeptidase, creatinine, sodium, potassium, C-reactive peptide Heparin (4.9 mL) ß-hydroxybutyrate, free fatty acids Glucose fluoride (2.7 mL) Serum (7.5 mL) Insulin, pro-insulin, c-peptide, IL-1 Ra, IL-6 BD vacutainer K3E (5 mL, 15%, Aprotinin 250 KIU plus DPP4-inhibitor) Glucagon, GLP-1
Volume	10.3 mL	30.4 mL
Total volume 71.1 mL		

ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; IL-6, interleukin-6; IL-1Ra, Interleukin-1 receptor antagonist.

or need for hospitalisation and if regarded as medically relevant).

Start of treatment phase (visit 2, day 1, 1.5 h)

Patients need to arrive fasted after an 8-hour fasting period. Adverse events and changes in medication will be documented. Vital signs will be documented, and a blood sample will be drawn (see visit 2 table 2). A blinded Dexcom G6 sensor will be placed and patients will receive a diary for daily documentation of hypoglycaemic episodes, including symptoms, circumstances, severity (glucose level, required assistance), treatment and outcome. The first dose of the study medication will be administered in the study centre. In addition, patients will be asked about their quality of life (SF-36 questionnaire), fear of hypoglycaemic episodes and hypoglycaemia awareness (modified Clark score).[24]

Interim visits (visit 3 between days 8 and 10 and visit 4 between days 18 and 20, each 0.5 hour). At each visit, a new Dexcom G6 sensor will be placed, and diary documentation and adverse events will be assessed.

End of treatment phase (visit 5, day 29, 1.0 h)

Patients arrive after an 8-hour fasting period. Dexcom G6 sensor will be removed, and glucose readings will be recorded along with data from the diary. QoL (SF-36 questionnaire), number and severity of hypoglycaemic episodes will be assessed. Adverse events will be systematically documented. A blood sampling (see visit 5 table 2) will be performed. Fear of hypoglycaemic episodes, hypoglycaemia awareness and concomitant medication will be assessed.

Follow-up visit (visit 6, day 90, 0.5 h)

A follow-up visit will be done 2 months after the treatment period, including the assessment of QoL (SF-36), hypoglycaemia awareness, fear of hypoglycaemia, concomitant medication and adverse events.

STUDY POPULATION

Eligibility criteria

Participants fulfilling all of the following inclusion criteria are eligible for the study:

- Patients after bariatric surgery (ie, sleeve gastrectomy, RYGB, omega-loop bypass, biliopancreatic diversion) with documented hypoglycaemia, that is, <3.0 mmol/L and at least five hypoglycaemic episodes per week despite dietary modification
- Age 18–75 years
- For women with childbearing potential, willingness to use contraceptive measures adequate to prevent pregnancy during the study
- Informed consent as documented by signature

The presence of any one of the following criteria will lead to exclusion of the participant:

- Current diagnosis of any type of diabetes mellitus according to ADA criteria
- Intolerance to the study drug
- Signs of current infection
- Any use of immunosuppressive medication
- Use of any drug therapy for postbariatric hypoglycaemia apart from acarbose (all remaining drugs have to be discontinued four half-life times before screening phase)
- Unstable or supraphysiologic glucocorticoid therapy
- Neutropenia (leucocyte count <1.5 × 109/L or ANC<0.5 × 109/L)
- Anaemia (haemoglobin <11 g/dL for males, < 10 g/dL for females)
- Clinically significant kidney or liver disease (creatinine >1.5 mg/dL, AST/ALT>2 × ULN, alkaline phosphatase >2 × ULN, or total bilirubin > 1.5 × ULN)
- Uncontrolled congestive heart failure
- Uncontrolled malignant disease
- Currently pregnant or breastfeeding
- Known or suspected non-compliance, drug or alcohol abuse
- Meeting the criteria for vulnerability (eg, participants incapable of judgement or participants under tutelage)

- Inability to follow the procedures of the study, for example, due to language problems, psychological disorders, dementia, etc.
- Participation in another clinical trial using investigational drugs in the last 30 days or planned participation in the next 90 days
- Previous enrolment into the current study

Enrolment of the investigator, his/her family members, employees and other dependent persons.

STUDY ASSESSMENTS

Study flow chart/table of study procedures and assessments

Please refer to table 1. and figure 1.

Assessments of outcomes

5.2.1 Assessment of primary and secondary outcomes

Continuous glucose data will be collected using Dexcom G6 sensors with a blinded reader. Data will be analysed by an independent third party. Hypoglycaemic episodes will be self-reported using an online or paper-based diary based on the patient's preference.

5.2.2 Assessment of safety outcomes

All adverse events (AEs) and all serious adverse events (SAEs) will be recorded and fully investigated based on observed or voluntarily reported signs and symptoms as well as findings in the participant's physical examination and/or laboratory results. All AEs (category I–V) will be documented according to Common Terminology Criteria for Adverse Events (CTCAE v5.0).

5.2.3 Assessment of laboratory parameters

Laboratory parameters assessed throughout the study are outlined in table 2.

STATISTICAL METHODS

Hypothesis

We hypothesise that treatment with canakinumab in patients after bariatric surgery with postprandial hypoglycaemia leads to

- better quality of life (mental health), that is, an improvement of at least seven points on the SF-36 MCS or
- better quality of life (physical health), that is, an improvement of at least seven points on the SF-36 PCS or
- fewer hypoglycaemic events (defined as glucose values below 3.0 mmol/L), that is, a relative risk reduction by 20% or more.

Demonstration of a relevant improvement on at least one of these three outcomes at the end of the treatment phase (visit 5, day 29) is considered sufficient to guide clinical decisions and establish statistical superiority of the canakinumab treatment versus placebo.

The null hypothesis is that there will be no difference in QoL (MCS or PCS) or in the risk for hypoglycaemic events between canakinumab and placebo. The alternative hypothesis is that there will be a difference.

Determination of sample size

We are not aware of an established minimal clinically important difference (MCID) for health-related QoL in this patient population. Based on a systematic review by Mouelhi *et al* reporting MCIDs in the SF-36 used in studies in the area of rheumatology and neurology/neurovascular disease in a range of 4.1 to 5.2[25] and 4.0 to 9.6 points,[26] as well as further diabetes and pulmonology studies reporting MCIDs in a range of 2 to 7 points,[27–29] we determined a difference of at least seven points clinically relevant for the mental health and the physical health component of the SF-36.

For the endpoint 'reduction of hypoglycaemic events,' we estimated that during 28 days of treatment with canakinumab, a relative reduction by 20% would be clinically meaningful compared with placebo, given at least five hypoglycaemic episodes at baseline.

The study's sample size was calculated to maintain a family-wise error rate of ≤5% and a power of ≥95%, based on a minimum absolute treatment effect of 7 points on PCS and MCS, a 20% relative reduction in hypoglycaemic episodes and an average of five episodes per week in the placebo group.

Estimations used Wilcoxon–Mann–Whitney tests, Poisson distributions for hypoglycaemic episodes and Hypo-BEAR study data for PCS and MCS.[20] The Holm–Bonferroni method was used to control the family-wise error rate.

Assuming a 10% dropout rate, 62 patients should be recruited to obtain at least 54 evaluable participants (28 per group), providing 95% power for showing a difference in at least one of the three endpoints and 81% power for showing a difference in at least one of the two QoL endpoints, which we considered most significant for patients. The power for detecting differences in individual outcomes was 91% for the number of hypoglycaemic episodes, 68% for PCS and 49% for MCS.

Planned analyses

All analyses will be conducted using the statistical software package R[30] using 'two-sided' statistical tests and confidence intervals with standard significance and confidence levels 5% and 95 %, respectively.

More detailed information on analyses will be provided in a statistical analysis plan, which will be created before any statistical analysis takes place. Any deviation from the original statistical plan will be described and justified in the protocol and reported to the ethical committee.

6.3.1 Datasets to be analysed, analysis populations

The full analysis set (FAS) will include all patients who were randomised. The per protocol set (PPS) will include all patients in the FAS who fulfilled the eligibility criteria and for whom the treatment and follow-up were completed as planned in the study protocol.

All statistical analyses will be performed on the FAS according to the intention-to-treat principle (ie, all patients will be analysed on the basis of the intervention to which they were randomly allocated), except for sensitivity analyses performed on the PPS (where we fully acknowledge the risk of bias surrounding naïve per-protocol analyses).[31]

Categorical data will be presented as absolute and relative frequencies (with the differences between study arms analysed by Pearson's chi-squared tests). For each numerical variable, the mean and SD or the median and IQR will be presented, as appropriate, with the difference between study arms analysed by Student's t-test for parameters presumed to be normally distributed or Wilcoxon–Mann–Whitney test for those that are not assumed to follow a normal distribution.

6.3.2 Primary analysis

Treatment effects on PCS, MCS and number of hypoglycaemic episodes will be tested by Wilcoxon–Mann–Whitney tests. The Holm–Bonferroni method will be used to control the family-wise error rate at the 5% level.

Sensitivity analyses will be performed on the PPS as well as by (generalised) linear models with study arm, corresponding baseline values, study centre, age and sex as covariates.

Missing values will be handled by available-case analyses.

6.3.3 Secondary analyses

Treatment effects on the secondary endpoints will be tested by Wilcoxon–Mann–Whitney tests. Descriptive statistics will be used to summarise the adverse events.

Continuous glucose monitoring data will be analysed using the R software package (version 3.6.0).

The primary and secondary analyses will be repeated on the subgroups defined by sex. Furthermore, the (generalised) linear model analyses will also be performed with the interaction of sex and study arm as an additional covariate.

6.3.4 Interim analyses

There will be one interim analysis after the first 30 patients by an independent statistician at the clinical trial unit (CTU) at the University Hospital Basel for futility and safety. Data will be assessed by an independent safety monitoring board.

6.3.5 Safety analysis

Safety will be assessed via a rigorous and detailed examination of adverse events and serious adverse events at each visit.

A pregnancy test will be conducted in all female participants of reproductive age to rule out pregnancy prior to study start. Appropriate contraception for this study comprises the use of condoms and either intrauterine devices or 3-monthly contraceptive injection or birth control pill.

There will be no rescue medication.

6.3.6 Concomitant interventions

Any used medication and changes in medication will be recorded in the CRF. No additional antidiabetic or anti-inflammatory medication is allowed before or during active study intervention phase (4-week period), as well as no strict diet (low-carb/ketogenic diet) since this may influence any outcome parameter.

Handling of missing data and dropouts

Results will be summarised using all available data. Multiple attempts will be made to obtain missing data. Dropouts will not be replaced.

Further handling of missing data will be specified in the detailed analysis plan.

QUALITY ASSURANCE AND CONTROL

Data handling and record keeping/archiving

A subject screening and enrolment log will document all eligible and non-eligible participants, including reasons for exclusion. For enrolled subjects, case report forms (p-CRFs) will be completed and signed by the principal investigator or co-investigator, using either source documents or direct entries. All study-related documents, including p-CRFs, consent forms and logs, must be retained for at least 10 years poststudy.

Participants are assigned unique IDs comprising a three-digit study centre prefix and a subject-specific three-digit number, with no personal identifiers included in the p-CRFs.

Source documents will detail critical study data (eg, visit dates, consent forms, adverse events and exam results) to confirm participants' existence and document medical history. All study data and related documents must be securely archived for the mandatory 10-year period following study completion.

Data management

7.2.1 Data management system

The study data collected in the p-CRF will be transferred to a web-based electronic data capture (EDC) system, REDCap. The EDC system runs on a server maintained by the IT department of the University Hospital Basel. Authorised persons at the study site are responsible for data entry into the EDC system.

7.2.2 Data security, access and backup

The EDC system is accessible via a standard browser on an internet-connected device. Password protection ensures that only authorised persons can enter the system to view, add or modify data according to their permissions.

Data will be handled with utmost discretion and is only accessible to authorised personnel who require the data to fulfil their duties within the scope of the research project. On the eCRFs and other project-specific documents, participants are only identified by a unique participant number.

The measurement data are stored in the eCRF of REDCap, and the system is secured with automatic backup via the servers of the Department of Clinical Research of the University Hospital Basel.

7.2.3 Analysis and archiving

The electronic data capture (EDC) system will be locked after all data was monitored and all raised queries have been resolved.

The data will be exported and archived by the investigator.

Source data/documents, eCRFs will be stored at study site for at least 10 years and be destroyed thereafter.

7.2.4 Data validation, monitoring and oversight

Data entered into the eCRF is automatically validated for completeness and discrepancies, with an audit trail tracking all entries and changes.

The study will be monitored by a qualified, independent monitor from the University Hospital Basel through one initiation visit, two routine visits and one closeout visit. The monitor will access and review source data, raise queries via a query management system and address these queries during visits. Designated investigators must respond to these queries for resolution.

An independent data safety monitoring committee (DSMC) from the CTU at the University of Basel, Basel, Switzerland, will oversee the trial, as well as conduct interim analyses after 30 patients and advise the sponsor on trial continuation based on statistical analyses of safety data and on expert consensus. Trial data access is limited to the DSMC, and safety data is kept confidential to prevent bias.

If safety concerns arise, the sponsor will immediately notify all investigators and the local ethics committee. The sponsor reserves the right to temporarily suspend or prematurely discontinue this trial either at a single site or at all sites at any time.

Data generated by this study must be available for inspection on request by representatives of the appropriate national and local health authorities, and the local ethical committee.

Confidentiality and data protection

All personal and medical information obtained for this study is confidential, and disclosure to third parties other than those noted below is prohibited. Participant's data will be identified by study and subject ID number.

On the participant's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for her or his welfare.

SUPPLEMENTS

Fear of hypoglycaemia scale

The fear of hypoglycaemia will be assessed by using a 10-cm long visual analogue scale graded from '0–no fear at all' to '10–massive fear' (online supplemental file). Patients will be asked to rate their fear of hypoglycaemia at baseline and at the end of the 4-week intervention phase and at follow-up. A scale on the back is used for numerically measuring the respective response of the participant.

Patient diary

Online supplemental file.

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Contributors MD is the sponsor-investigator of the trial and procured funding. MD is the guarantor. MH wrote the first draft of the protocol. MC, MD, LB and DH critically reviewed the protocol and revised the methodology. MC prepared the statistical analysis plan and reviewed by MH and MD. MH registered the study. MH coordinates the study. JF set up the REDCap database. MH, JF and AF are involved in the recruitment of patients and patient care. JF prepared the first draft of the 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 The design of the study, including the choice of outcomes and study duration, was informed by literature research and an online questionnaire distributed to patients with postbariatric hypoglycaemia.[7] Additionally, the study was promoted via patient advocate groups. Once completed, findings will be presented at congresses and patient education events.

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REFERENCES

1 Lee CJ, Clark JM, Schweitzer M, *et al*. Prevalence of and risk factors for hypoglycemic symptoms after gastric bypass and sleeve gastrectomy. *Obesity (Silver Spring)* 2015;23:1079–84.
2 Kefurt R, Langer FB, Schindler K, *et al*. Hypoglycemia after Roux-En-Y gastric bypass: detection rates of continuous glucose monitoring (CGM) versus mixed meal test. *Surg Obes Relat Dis* 2015;11:564–9.
3 Roslin MS, Oren JH, Polan BN, *et al*. Abnormal glucose tolerance testing after gastric bypass. *Surg Obes Relat Dis* 2013;9:26–31.
4 Lupoli R, Lembo E, Rainone C, *et al*. Rate of post-bariatric hypoglycemia using continuous glucose monitoring: A meta-analysis of literature studies. *Nutr Metab Cardiovasc Dis* 2022;32:32–9.
5 Roslin MS. Why it matters. A paired editorial for "Hypoglycemia after Roux-en-Y gastric bypass: detection rates of continuous glucose monitoring (CGM) versus mixed meal test". *Surg Obes Relat Dis* 2015;11:569–72.
6 Dreber H, Thorell A, Reynisdottir S, *et al*. Health-Related Quality of Life 5 Years After Roux-en-Y Gastric Bypass in Young (18-25 Years) Versus Older (≥26 Years) Adults: a Scandinavian Obesity Surgery Registry Study. *Obes Surg* 2019;29:434–43.
7 Hepprich M, Donath MY, Hemkens LG. Patient involvement to inform the design of a clinical trial in postbariatric hypoglycaemia. *BMC Med Res Methodol* 2020;20:290.
8 Vaurs C, Brun J-F, Bertrand M, *et al*. Post-prandial hypoglycemia results from a non-glucose-dependent inappropriate insulin secretion in Roux-en-Y gastric bypassed patients. *Metab Clin Exp* 2016;65:18–26.
9 Roslin M, Damani T, Oren J, *et al*. Abnormal glucose tolerance testing following gastric bypass demonstrates reactive hypoglycemia. *Surg Endosc* 2011;25:1926–32.
10 Nannipieri M, Belligoli A, Guarino D, *et al*. Risk Factors for Spontaneously Self-Reported Postprandial Hypoglycemia After Bariatric Surgery. *J Clin Endocrinol Metab* 2016;101:3600–7.
11 Goldfine AB, Mun EC, Devine E, *et al*. Patients with neuroglycopenia after gastric bypass surgery have exaggerated incretin and insulin secretory responses to a mixed meal. *J Clin Endocrinol Metab* 2007;92:4678–85.
12 Hazlehurst J, Khoo B, Lobato CB, *et al*. Society for Endocrinology guidelines for the diagnosis and management of post-bariatric hypoglycaemia. *Endocr Connect* 2024;13:e230285.
13 Patience N, Sheehan A, Cummings C, *et al*. Medical Nutrition Therapy and Other Approaches to Management of Post-bariatric Hypoglycemia: A Team-Based Approach. *Curr Obes Rep* 2022;11:277–86.
14 Øhrstrøm CC, Worm D, Hansen DL. Postprandial hyperinsulinemic hypoglycemia after Roux-en-Y gastric bypass: an update. *Surg Obes Relat Dis* 2017;13:345–51.
15 Rariy CM, Rometo D, Korytkowski M. Post-Gastric Bypass Hypoglycemia. *Curr Diab Rep* 2016;16:19.
16 Maedler K, Sergeev P, Ris F, *et al*. Glucose-induced beta cell production of IL-1beta contributes to glucotoxicity in human pancreatic islets. *J Clin Invest* 2002;110:851–60.
17 Meier DT, de Paula Souza J, Donath MY. Targeting the NLRP3 inflammasome-IL-1β pathway in type 2 diabetes and obesity. *Diabetologia* 2025;68:3–16.
18 Dror E, Dalmas E, Meier DT, *et al*. Postprandial macrophage-derived IL-1β stimulates insulin, and both synergistically promote glucose disposal and inflammation. *Nat Immunol* 2017;18:283–92.
19 Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. *Nat Rev Immunol* 2011;11:98–107.
20 Hepprich M, Wiedemann SJ, Schelker BL, *et al*. Postprandial Hypoglycemia in Patients after Gastric Bypass Surgery Is Mediated by Glucose-Induced IL-1β. *Cell Metab* 2020;31:699–709.
21 Compendium.ch. fachinformation ilaris (canakinumab). Available: https://compendium.ch/product/1357923-ilaris-inj-los-150-mg-ml/mpro [Accessed 21 May 2025].
22 Agency EM. Ilaris Product Information,
23 Ridker PM, Everett BM, Thuren T, *et al*. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. *N Engl J Med* 2017;377:1119–31.
24 Clarke WL, Cox DJ, Gonder-Frederick LA, *et al*. Reduced awareness of hypoglycemia in adults with IDDM. A prospective study of hypoglycemic frequency and associated symptoms. *Diabetes Care* 1995;18:517–22.
25 Carreon LY, Bratcher KR, Canan CE, *et al*. Differentiating minimum clinically important difference for primary and revision lumbar fusion surgeries. *J Neurosurg Spine* 2013;18:102–6.
26 Zhou F, Zhang Y, Sun Y, *et al*. Assessment of the minimum clinically important difference in neurological function and quality of life after surgery in cervical spondylotic myelopathy patients: a prospective cohort study. *Eur Spine J* 2015;24:2918–23.
27 Ward MM, Guthrie LC, Alba MI. Clinically important changes in short form 36 health survey scales for use in rheumatoid arthritis clinical trials: the impact of low responsiveness. *Arthritis Care Res (Hoboken)* 2014;66:1783–9.
28 Bjorner JB, Lyng Wolden M, Gundgaard J, *et al*. Benchmarks for interpretation of score differences on the SF-36 health survey for patients with diabetes. *Value Health* 2013;16:993–1000.
29 Jayadevappa R, Cook R, Chhatre S. Minimal important difference to infer changes in health-related quality of life-a systematic review. *J Clin Epidemiol* 2017;89:188–98.
30 R Foundation for Statistical Computing. A language and environment for statistical computing. Vienna, Austria, 2020.
31 Ewald H, Speich B, Ladanie A, *et al*. Marginal structural models and other analyses allow multiple estimates of treatment effects in randomized clinical trials: Meta-epidemiological analysis. *J Clin Epidemiol* 2019;107:12–26.