Effect of Hybrid Closed-Loop Insulin Delivery System on Glycemic Management in Perioperative Patients with Type 2 Diabetes Receiving Parenteral Nutrition: An Open-Label, Randomized Controlled Trial

Statistical Analysis Plan

Version 1.0

Protocol Version 1.0

Date: June 20, 2026

Contents

List of Abbreviations

Abbreviation	Full Item
FAS	Full Analysis Set
SS	Safety Set
Mean	Mean
CGM	Continuous Glucose Monitoring
NMPA	National Medical Products Administration
PN	Parenteral Nutrition
EN	Enteral Nutrition
PPS	Per Protocol Set
TIR	Time In Range
TAR	Time Above Range
TBR	Time Below Range
CV	Coefficient Of Variation
SAP	Statistical Analysis Plan
SD	Standard Deviation
AE	Adverse Event
SAE	Serious Adverse Event
ADE	Adverse Device Effect

1. Study Overview

This trial is an open-label, parallel-group, randomized controlled exploratory study.

2. Objectives

The main objective of this study is to investigate the impact of hybrid closed-loop (HCL) pump therapy on glycemic control in type 2 diabetes mellitus （T2DM） patients undergoing perioperative parenteral nutrition (PN), seeking to provide new insights and strategies for blood glucose management in this population.

3. Statistical Hypotheses

Our primary objective is to assess the impact of HCL pump therapy on perioperative T2DM patients requiring PN compared with that with open-loop (OL) pump therapy, therefore we will test the following statistical hypotheses

a. Null Hypothesis: There is no difference in the means of time spent in the 5.6-10.0mmol/L range between HCL Group and Control Group.

b. Alternative Hypothesis: There is a difference in the means of time spent in the 5.6-10.0mmol/L range between HCL Group and Control Group.

4. Sample Size

According to clinical expert assessment, a 20% difference between groups was hypothesized. Assuming a standard deviation of 20%, with a two-sided α level of 0.05 and 80% statistical power, we calculated a sample size of 16 participants per group. Accounting for an anticipated 20% dropout rate, 20 participants per group (total $N = 40$) were required.

Randomization will be performed using a 1:1 randomization scheme. A R program will be written to generate the randomization schedule.

5. Definition of Analysis Sets

The primary and secondary efficacy endpoints will be analyzed based on the Full Analysis Set (FAS) , with supportive analyses conducted using the Per-Protocol Set (PPS) . Safety analyses will be performed based on the Safety Analysis Set (SS).

5.1 Full Analysis Set (FAS)

The FAS is defined in accordance with the Intention-to-Treat (ITT) principle and includes all randomized subjects who have used the investigational device at least once, and who have at least one baseline measurement and at least one post-baseline efficacy assessment. Subjects will be analyzed according to the treatment group to which they were originally randomized.

5.2 Per-Protocol Set (PPS)

The PPS is a subset of the FAS and consists of subjects who completed the study without major protocol deviations or violations. The list of subjects excluded from the PPS will be determined prior to database lock. Exclusions from the per-protocol set include, but are not limited to, subjects receiving prohibited concomitant medications or those with major protocol deviations/violations.The exclusion criteria and rationale will be discussed in detail during the data review meeting prior to database lock.

5.3 Safety Analysis Set (SS)

The Safety Analysis Set (SS) consists of a subset of all participants who have received at least one dose of study treatment and for whom safety data are available in the database. Analyses will be based solely on the observed (actual) values obtained.

6. The distribution characteristics of subjects Analysis

1) Report the number of subjects enrolled and completing the trial, and define the analysis sets (FAS, PPS, SS).
2) Calculate the number and percentage of subjects enrolled, completing the trial, and prematurely discontinued; analyze reasons for subject discontinuation.
3) Conduct a classified analysis of reasons for exclusion from analysis sets, reporting subject counts and proportions by category.
4) Provide a detailed listing of population disposition, including reasons for non-inclusion in PPS, FAS, and SS.
5) Generate a subject disposition flowchart.

7. Description of Statistical Methods

All analyses will be conducted following the intention to treat (ITT) principle where all randomized participants are analyzed in their allocated treatment group whether or not they receive their randomized treatment. All baseline data will be presented descriptively, both overall and within treatment group, using mean (SD), median (minimum-maximum) or frequency (percentage), as appropriate. All statistical tests will use a 2-sided significance level of 5% (unless otherwise specified).

The Shapiro–Wilk test will be used to assess whether the outcome variables follow a normal distribution. The unpaired t-tests will be used to compare normally distributed variables and the Mann-Whitney U tests for highly skewed variables (this is expected for time below 70mg/dL, number of hypoglycemia, and possibly time above 360mg/dL). Categorical variables will be compared using Fisher's exact test.

For both primary and secondary endpoints, a mixed linear regression model will be employed to adjust for the effects of age, type of surgery and other potential confounding factors. Group differences will be compared, and 95% confidence intervals (CI) will be reported. Primary outcome and secondary outcomes will also be calculated for the overnight period (00:00 h to 05:59 h) and daytime period (06:00 h to 23:59 h) as exploratory analyses.

Statistical analyses were performed using IBM SPSS Statistics version 26.0 and SAS 9.4,. All statistical

analyses were conducted by a biostatistician, with consulted from a clinical trial unit statistician as needed

8. Efficacy Outcome Measures

8.1 Primary outcome

The primary outcome measure is time spent with CGM glucose concentration in the target range (5.6-10.0mmol/L) during the study period.

8.2 Secondary outcomes

The following outcomes during the surgical intervention period on the two treatment arms will be compared:

1）Time spent with CGM glucose concentration in the range (4.4-10.0mmol/L) measured by CGM.
2) Time above range (TAR) > 10.0 mmol/L (180 mg/dL): Percentage of time spent above 10.0 mmol/L (180 mg/dL) measured by CGM.
3) TAR > 20.0 mmol/L (360 mg/dL): Percentage of time spent above 13.9 mmol/L (250 mg/dL) measured by CGM.
4) Time below range < 5.6 mmol/L (100 mg/dL): Percentage of time spent above 3.9 mmol/L (70 mg/dL) measured by CGM.
5) Time below range (TBR) < 3.9 mmol/L (70 mg/dL): Percentage of time spent above 3.9 mmol/L (70 mg/dL) measured by CGM.
6) TBR < 3.0 mmol/L (54 mg/dL): Percentage of time spent above 3.0 mmol/L (54 mg/dL) measured by CGM.
7) TBR < 2.8 mmol/L (50 mg/dL): Percentage of time spent above 3.0 mmol/L (54 mg/dL) measured by CGM.
8) Mean sensor glucose measured by CGM.
9) Standard deviation of mean glucose（SD）: Standard deviation of sensor glucose measurements during CGM.
10) Coefficient of variation（CV）: Standard deviation divided by mean glucose level measured by CGM.
11) Glycemia risk index (GRI): Glycemia risk index will be calculated according to the following equation: GRI = (3.0×VLow) + (2.4×Low) + (1.6×VHigh) + (0.8×High).
12) Total daily insulin（TDD） (units/kg)
13) Daily basal insulin (units/kg)
14) Daily bolus insulin (units/kg)
15) preoperative preparation time(days)

9. Exploratory Analysis

During the overnight period between 00:00 h and 05:59 h (6 hours) and the daytime period between 06:00 h and 23:59 h (18 hours), the following outcomes will be calculated:

TIR 5.6-10.0mmol/L (70-180 mg/dL)
TIR 4.4-10.0mmol/L (80-180 mg/dL)
TAR > 10.0 mmol/L (180 mg/dL)
TAR > 20.0 mmol/L (360 mg/dL)

TBR < 5.6 mmol/L (100 mg/dL)
TBR < 3.9 mmol/L (70 mg/dL)
TBR < 3.0 mmol/L (54 mg/dL)
TBR < 2.8 mmol/L (50 mg/dL)
Mean sensor glucose
Standard deviation of mean glucose
Coefficient of variation
Glycemia risk index
Time in hours of CGM data

10.Safety Analysis

The incidence of adverse events will be summarized according to treatment group. All serious adverse events or those leading to study treatment discontinuation will be described in detail. Summarize changes from baseline in clinical laboratory parameters and vital signs at scheduled visits, stratified by treatment group

Safety data included the incidence of perioperative infection, *hypoglycemia (level 1 hypoglycemia, level 2 hypoglycemia, severe hypoglycemia),incidence of diabetic ketosis and adverse events rate including equipment failures and serious adverse events

Formal statistical testing only will be performed for selected safety endpoints. For the following outcomes, Categorical variables (such as AE rate) were reported as frequency (n) and percentage (%).The Cochran-Mantel-Haenszel chi-square test (with adjustment for center effect) or Fisher's exact test (for small samples) was used for dichotomous variables.

- adverse event rate(including incidence of hypoglycemia and incidence of diabetic ketosis)

- serious adverse events rate
- the incidence of perioperative infection
- the incidence of adverse event of the device

*Level 1 hypoglycemia is a glucose concentration < 70 mg/dL (3.9 mmol/L). Level 2 hypoglycemia is a blood glucose concentration <54 mg/dL (3.0 mmol/L),Level 3 hypoglycemia, also known as severe hypoglycemia, has no specific threshold and is a clinical event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery.

11.Baseline Descriptive Statistics

Baseline demographic and clinical characteristics of the cohort of all randomized participants will be summarized in a table using summary statistics appropriate to the distribution of each variable. Descriptive statistics will be displayed overall and by randomization group.

Will include:

- Age in years
- Gender

- BMI
- diabetes duration in years
- HbA1c
- Diabetes Therapy before enrollment (Oral antidiabetic drugs and/or Insulin)
- Type of surgery
- Type of parenteral nutrition solution
- Duration of parenteral nutrition
- Postoperative Clavien-Dindo classification of complications

12.Data Management and Quality Control

12.1 Data Collection

Data on subjects' demographic characteristics (age, gender, height, weight, etc.), current and past medical history, inflammatory markers, and types of nutritional solutions, will be collected using Case Report Forms (CRFs). Continuous glucose monitoring (CGM) data from both the intervention and control groups will be stored and downloaded from cloud-based platforms. All information will be remained fully traceable. Missing values will not be imputed during the analysis.

12.2 Data Management Plan

Develop a detailed data management plan (DMP) encompassing processes for data collection, processing, storage, and backup to ensure data accuracy and integrity.

12.3 Data Quality Control

Rigorous quality control measures will be implemented throughout data collection, processing, and analysis, including source data verification, validation checks, and blind data review, to ensure the reliability and validity of statistical analysis results

13.Interpretation and Reporting of Statistical Analysis Results

13.1 Interpretation of Results

Statistical results will be interpreted using appropriate terminology, with emphasis on whether the differences between the two treatment groups are statistically significant.

13.2 Reporting of Results

Based on the statistical analysis, a clinical trial conclusion will be drawn to evaluate the application of the hybrid closed-loop artificial pancreas system in the management of patients receiving parenteral nutrition during the perioperative period.

14.References

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