STUDY PROTOCOL and STATISTICAL ANALYSIS PLAN

Title: Evaluating AI-Assisted Remote Optimization of Insulin Pump Settings in Type 1 Diabetes using CGM

NCT Number: Not yet assigned

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1. Study Design

This is a two-cohort, investigator-initiated, prospective clinical study.

- **Cohort 1 (Inpatient Cohort)**: A single-arm, open-label, inpatient feasibility study. A separate group of hospitalized adults with T1D will receive Artificial Intelligence (AI) -assisted insulin pump parameter optimization over 5–7 days under continuous clinical supervision. The objective is to assess acute safety and procedural feasibility.
- **Cohort 2 (Home-based Cohort)**: A separate group of outpatients with T1D will be randomized 1:1 to a two-period crossover design (two 4-week treatment periods, separated by a at lease 1-week washout if applicable). Participants will receive either AI-assisted remote parameter optimization or conventional sensor-augmented pump therapy in a crossover manner. The objective is to evaluate efficacy and safety of AI-assisted optimization in the home setting.

2. Primary Objective

To compare the change in Time-in-Range (TIR, 70–180 mg/dL) between AI-assisted optimization and conventional therapy during the home-based crossover period (Cohort 2).

3. Key Eligibility Criteria

Inclusion:

- Clinical diagnosis of T1D (with ⩾2 years documented duration or confirmatory criteria including islet autoantibodies, low C-peptide, or age of onset <15 years);
- Age 14–65 years;
- HbA1c < 11.0%;
- On multiple daily insulin injections (MDI) or insulin pump therapy for ⩾3 months;

Exclusion:

- Severe hypoglycemia or Diabetic Ketoacidosis (DKA) within 6 months;
- Presence of significant acute or chronic complications, hepatorenal disease, or other systemic diseases at screening. Hyperthyroidism or hypothyroidism with unstable thyroid function at the time of screening;
- Use of non-insulin glucose-lowering agents within 8 weeks (requires 7-day washout);
- Pregnancy, lactation, or ineffective contraception in women of childbearing potential;
- Active cardiovascular or cerebrovascular disease within 1 year;
- Any condition judged by the investigator to interfere with study participation.

4. Interventions

- **Experimental**: AI-Assisted Insulin Pump Settings Optimization System (cloud-based software generating weekly pump setting recommendations, reviewed and approved by a physician prior to implementation).
- **Control**: Conventional Sensor-Augmented Insulin Pump Therapy (dose adjustments per standard clinical practice, without AI assistance).

5. Outcome Measures

Primary (Cohort 2):

- Change in Time-in-Range (70–180 mg/dL) between AI-assisted and conventional periods.

Secondary (Cohort 2):

- Secondary efficacy outcomes: Time Below Range (TBR) (<3.9 and <3.0 mmol/L), Time Above Range （TAR）(>10.0 and >13.9 mmol/L), mean sensor glucose, glycemic variability (Standard Deviation (SD), Coefficient of Variation (CV)), total daily insulin dose, and HbA1c change.
- Safety outcomes: severe hypoglycemia events, DKA, device-related defects, Adverse Event/Serious Adverse Event.
- Adherence and satisfaction outcomes: physician acceptance rate, patient adherence rate, participant and investigator satisfaction questionnaires.

Other Pre-specified (Cohort 1):

- Inpatient feasibility and safety metrics (TIR, hypoglycemia/hyperglycemia events,

physician acceptance rate during inpatient stay).

6. Statistical Considerations

6.1 Primary Endpoint Analysis

The primary endpoint is the change in Time-in-Range (TIR, 70–180 mg/dL) comparing AI-assisted optimization versus conventional therapy in the home-based crossover cohort (Cohort 2). The TIR metrics for comparative analysis were derived from CGM data collected during the final 2 weeks of each 4-week treatment period

The primary analysis will use a linear mixed-effects model with fixed effects for treatment (AI vs. control), period, and baseline TIR, and a random effect for participant. The treatment effect will be estimated as the least-squares mean difference, with a two-sided 95% confidence interval. Statistical significance will be declared at $p < 0.05$.

6.2 Secondary Endpoint Analyses

Secondary efficacy endpoints (TBR, TAR, mean glucose, SD, %CV, total daily insulin, HbA1c) will be analyzed using analogous linear mixed-effects models or paired t-tests, as appropriate.

Safety endpoints (severe hypoglycemia, DKA, device defects, AEs/SAEs) will be summarized descriptively by treatment group, with incidence rates and 95% confidence intervals reported.

Adherence and satisfaction outcomes will be analyzed using descriptive statistics and, where applicable, Wilcoxon signed-rank tests.

6.3 Sample Size Justification

Based on prior literature, a sample size of 9 participants per sequence (total N=18 in Cohort 2) provides 80% power at a two-sided alpha of 0.05 to detect a 10% difference in TIR, assuming a standard deviation of 12%.

6.4 Handling of Missing Data

Missing data will be handled using multiple imputation or, if minimal, complete-case analysis. Sensitivity analyses will be conducted to assess the robustness of results to missing data assumptions.

6.5 Subgroup Analyses

Prespecified subgroup analyses will be conducted by baseline HbA1c, age group, or prior pump or CGM use.

6.6 Interim Analysis

No interim analysis is planned.

7. Study Duration

Total study duration is approximately 11 weeks per participant in Cohort 2 (4-week treatment period 1 + ≥1-week washout + 4-week treatment period 2), plus a 1-week screening period. Cohort 1 participants will complete the inpatient stay of 5–7 days.

8. Data Monitoring and Safety

An independent Data and Safety Monitoring Board (DSMB) will oversee safety. All algorithm-generated recommendations are subject to physician review and approval before implementation. Adverse events will be monitored throughout.