F3Z-MC-IORW Statistical Analysis Plan (1)

Assessment of Participant Adherence and Glucose Control While Using a Connected Insulin Management Platform

NCT05893797

Approval Date: 16-Aug-2023

Title Page

Protocol Title: Assessment of Participant Adherence and Glucose Control While Using a Connected Insulin Management Platform

Protocol Number: F3Z-MC-IORW (18171)

Compound Number: LY8888AX, LY275585

Short Title: Not Applicable

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana USA 46285

Regulatory Agency Identifier Number(s)

Registry	ID
EU Trial Number	2022-A02807-36

Document ID: VV-CLIN-124022

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Version History

This Statistical Analysis Plan (SAP) for Study F3Z-MC-IORW is based on the protocol dated 29 June 2023.

Table 1. SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	See date on Page 1	Not Applicable	Original version

1. Introduction

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for protocol F3Z-MC-IORW (Assessment of Participant Adherence and Glucose Control While Using a Connected Insulin Management Platform). This study is being completed to assess participant adherence and glucose control while using a connected insulin management platform in adults diagnosed with type 1 (T1D) or type 2 diabetes (T2D) on basal-bolus insulin therapy with glycated haemoglobin (HbA1c) ≥8%.

The purpose of this SAP is to outline the planned analyses in support of the clinical study report (CSR) for protocol F3Z-MC-IORW. Exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc, or unplanned, analyses not identified in this SAP will be clearly identified in the respective CSR.

There are no changes to the analyses described in the protocol.

1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
To compare the number of missed bolus doses (MBDs) during the last weeks of the unmasked Study Period 2 (Weeks 15 to 18), compared to the last weeks of the masked Study Period 1 (Weeks 5 and 6) in participants using the • Humalog® Tempo™ Pen • Tempo Smart Button™ • Glooko® Research Mobile Application (RMA), and Dexcom G6 Continuous Glucose Monitoring (CGM) system.	Difference in the average number of MBDs per week in the masked versus unmasked portions of the study. MBD is defined as no insulin dose from 1 hour prior to through 1 hour after the start of a glucose excursion (meal), where a glucose excursion is defined as a >70 mg/dL (>3.9 mmol/L) rise within 2 hours, not preceded by a value <70 mg/dL (<3.9 mmol/L).
Secondary	
• To evaluate difference in participant CGM time in range (TIR) (≥70 mg/dL to 180 mg/dL) in Study Period 1 versus Study Period 2. • To evaluate difference in participant CGM time above range (TAR) (>180 mg/dL and >250 mg/dL) in Study Period 1 versus Study Period 2.	• CGM TIR (≥70 mg/dL to 180 mg/dL) in the masked versus unmasked portions of the study • CGM TAR (>180 mg/dL and >250 mg/dL) in the masked versus unmasked portions of the study • CGM TBR (54 mg/dL ≤ TBR < 70 mg/dL and <54 mg/dL) in the masked versus unmasked portions of the study

Objectives	Endpoints
• To evaluate difference in participant CGM time below range (TBR) (54 mg/dL ≤ TBR < 70 mg/dL and <54 mg/dL) in Study Period 1 versus Study Period 2. • To evaluate Coefficient of Variation and mean sensor glucose from CGM values in Study Period 1 versus Study Period 2. • To examine occurrence and change in frequency of mistimed boluses per week between Study Period 1 versus Study Period 2. • To evaluate the change in total insulin doses (basal, mealtime per meal type, and correction bolus) between Study Period 1 versus Study Period 2. • To evaluate occurrence, change and Study Period 1 versus Study Period 2 change in correction boluses. • To examine the association between MBD and TIR, TAR, TBR, and HbA1c • To examine the association between mistimed bolus and TIR, TAR, TBR, HbA1c. • To assess device preference, satisfaction, convenience, and ease of use.	• Coefficient of variation and mean sensor glucose from CGM data collected from each participant • Occurrence and change of mistimed boluses • Total insulin dose per day, basal dose and insulin dose per type of meal (breakfast [B], lunch [L], snacks, and dinner [D]) as well as corrections doses • Occurrence, change, and masked versus unmasked change in correction boluses • CGM curves integrated with data received from the Tempo Pen to examine the association between MBD and TIR, TAR, TBR, and HbA1c • CGM curves integrated with data received from the Tempo Pen to examine the association between mistimed bolus and TIR, TAR, TBR, and HbA1c • Participant and healthcare professional (HCP) questionnaires.
Exploratory	
• To evaluate change in HbA1c from baseline to Visit 7. • To evaluate change in HCP views on a connected diabetes management platform. • To evaluate change in participant views on a connected diabetes management platform. • To carry out analysis for calculation of MBDs.	• Summary statistics of actual and change in HbA1c between baseline and Visit 7 • Outcome of Study F3Z-MC-IORW (IORW) HCP questionnaires • Outcome of Study IORW participant questionnaires • CGM curves integrated with data received from the Tempo Pen/Smart Button

Objectives	Endpoints
• To determine participant interaction with the mobile application and its correlation with MBD change between Study Period 1 versus Study Period 2. • To determine participant CGM wear time and correlation with MBD change between Study Period 1 versus Study Period 2. • To evaluate participant's fear of hypoglycaemia and its correlation with MBD. • To evaluate participant's daytime and nighttime CGM profiles during the 2 periods.	• Glooko Mobile Application use data (for example, number of connections to the application, number of uploads from CGM, number of CCI data coming from Tempo Smart Button, % of CGM data available, and number of manual insulin dose records) and comparison of Study Period 1 and Study Period 2 application use • Summary of CGM wear time data and correlation with MBD data and differences between Study Period 1 versus Study Period 2 • Hypoglycaemia Fear Survey – Short Form (HFS-SF) questionnaire scores will be summarized between Visit 1 and Visit 7 and correlated with MBD data. • Summarize nighttime (0000 hours to 0600 hours) versus daytime CGM profiles during the masked/unmasked periods.

1.2. Study Design

1.2.1. Overall Design

Study F3Z-MC-IORW (IORW) is a multicenter, open-label, controlled, single-arm pragmatic outpatient study in participants with T1D or T2D that comprises of 2 study periods, including:

- a 6-week run-in period (Study Period 1) when insulin timing and dosage data CCI [redacted] is masked to the participant using the Glooko® Research Mobile Application (RMA) and is unmasked to the healthcare professional (HCP) using the Glooko HCP platform, and
- a 12-week intervention period (Study Period 2) when insulin timing and dosage data CCI [redacted] is unmasked to the participant using the Glooko RMA and the HCP using the Glooko HCP platform.

Study IORW will be carried out in France and will include up to 10 clinical study sites. The study is expected to last approximately 16 months, with each participant duration of approximately 18 weeks. Approximately 50 participants will be enrolled in the study. Best efforts will be made to enroll a participant ratio of 4:1 for participants with T1D to participants with T2D.

1.2.1.1. Study Period 1 (Run-in) – Weeks 1 to 6 (Baseline)

Following the screening, the participants who meet study criteria will:

- receive sponsor-provided Humalog® Tempo™ Pen and Tempo Smart Button, Dexcom G6 Continuous Glucose Monitoring (CGM) system, and study-specific Android smartphone, and
- be instructed on how to use the study platform and will receive guidance from the study team on the use of the real time CGM data on the receiver to help them manage diabetes and insulin dosing. They will be trained on how to upload their CGM data on the Glooko RMA.

During that study period, mealtime insulin timing and dosage data CCI [redacted] will not be visible (masked) to the participant using Glooko RMA. Mealtime insulin details CCI [redacted] will be visible (unmasked) to the HCP using the HCP platform. They will also be allowed to track the basal insulin time and dosing and other data (for example, meals and exercise) manually in the RMA. Baseline (Visit 1 and Visit 3) study questionnaires will also be completed.

Participants will be asked to follow their pre-insulin study regimen (as prescribed by the investigators), lifestyle, and behavior. It is recommended that the site does not interact with the participant with respect to their Glooko RMA during the masked Study Period 1 unless required for participant safety. The study participant and HCP will not communicate, outside of the scheduled visit and activities, except in cases of acute complication, adverse event (AE) and device deficiency (DD) reporting, or need for technical support.

Following Study Period 1 (during Visit 3), mealtime insulin timing and dosage data CCI [redacted] will be unmasked to the study participant by the HCP. The study participant and HCP will then review and discuss together the data collected during Study Period 1, including the potential reasons for suboptimal glucose control. The HCP will be able to propose any educational activities to be taken during Study Period 2 that would result from the review of the Glooko platform report, including insulin dose adjustments and other advices deemed appropriate (for example, missing bolus doses, late injection timing, and carb counting).

1.2.1.2. Study Period 2 (Intervention) – Weeks 7 to 18

Following Study Period 1, the participants will enter the 12-week Study Period 2 during which insulin timing and dosage data CCI [redacted] will be visible (unmasked) to the participant and HCP in the Glooko RMA and HCP platform. Throughout the entire Study Period 2, data from the Humalog Tempo Pen/Smart Button CCI [redacted] will be transferred to the Glooko RMA. Participants should continue to periodically upload Dexcom G6 CGM during Study Period 2.

HCPs can monitor participant adherence through the HCP portal. The participant list displays the date of last sync for each to determine the last Tempo Pen/Tempo Smart Button connection. If necessary, the study site will follow-up with participants to ensure adequate duration of CGM wear and timely Tempo Pen/Smart Button study data transfer to the Glooko RMA.

1.2.1.3. Safety Follow-up

Following completion of Study Period 2, study participants will complete their safety follow-up period.

Figure 1.1 gives an outline of the study schema.

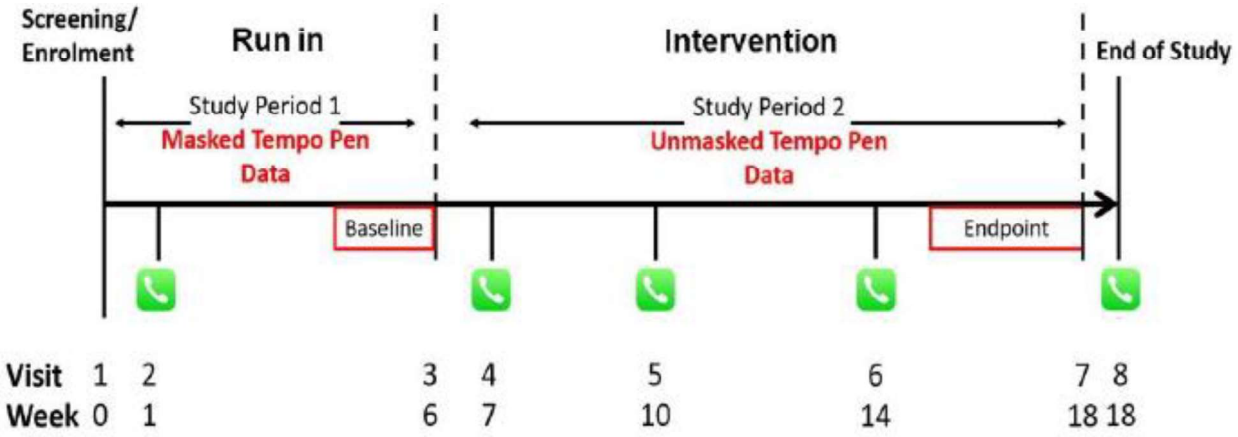


Figure 1.1. Study schema.

2. Statistical Hypotheses

The primary objective of this single-arm study is to compare the number of missed bolus doses (MBDs) during the masked and unmasked application periods in participants with T1D and T2D via the Tempo Pen with Tempo Smart Button and on the CGM system.

The primary analyses will be conducted at the end of the clinical study on data collected from all participants.

Thus, the null hypothesis to be tested in relation to the primary endpoint is as follows:

- Study Period 2 is not different from Study Period 1 with respect to MBDs.

2.1. Multiplicity Adjustment

A p-value of ≤ 0.05 will be considered statistically significant. No adjustments for multiplicity will take place.

3. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Main Analysis Set	All continuous glucose monitoring (CGM) data should be included in the final analysis, but the proportion of participants who met the minimum 70% data-obtainment requirement during 14 days should be reported as part of the data completeness. Participants with ≥70% of CGM data present for a particular day will be considered complete for the day or valid CGM day. Similarly daytime and nighttime periods will be checked separately for valid CGM period. Following the guidelines of the Advanced Technologies and Treatments for Diabetes (ATTD) consensus on CGM use, only participants with at least 10 days' worth of valid CGM data out of the last 14 days (Weeks 5 and 6) in the masked application period will be considered for the main analysis set (Danne et al. 2017; Battelino et al. 2023). Among these participants, only participants that satisfy the below criteria for the unmasked application period will be considered as evaluable participants and included in the main analysis set: • participants with at least 20 of 28 days' worth of CGM data (Weeks 15 to 18), or • participants discontinuing early that have at least 20 days' worth of CGM data in the whole unmasked application period (Weeks 7 to 18). Efficacy analyses will be carried out on the main analysis set. To allow for this clinical trial to be generalizable to the wider population and to prevent the chance of analyzing a biased set of "only adherent" participants, efficacy analyses will be repeated on the sensitivity analysis set.
Sensitivity Analysis Set	The sensitivity analysis set includes all participants in the main analysis set, plus participants with at least 10 days' worth of CGM data in the whole masked application period (Weeks 1 to 6), and all participants with at least 20 days' worth of CGM data in the whole unmasked application period (Weeks 7 to 18).
Safety Analysis Set	Safety analyses will be carried out on the Safety Population, which consists of all participants with at least 1 measurement in the masked application period and/or unmasked application period.

4. Statistical Analyses

4.1. General Considerations

The study will use a frequentist approach to statistical analysis. Descriptive statistics for continuous variables will entail mean, standard deviation (SD), minimum, median, and maximum. Descriptive statistics for categorical variables will include frequency and percentage.

Efficacy analyses will be conducted on the Main Analysis Set and repeated on the Sensitivity Analysis Set. Safety analyses will be conducted on the safety analysis set, unless otherwise stated.

Any change in the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the CSR. Additional exploratory analyses of the data will be conducted, as deemed appropriate.

Analysis data sets, statistical analyses and associated output generated by Lilly will be generated using SAS® Software version 9.4 or later.

4.2. Participant Dispositions

The number and percent of participants in each analysis population will be presented with percentages based on the Safety Population.

Additionally, participant allocation will be summarized in a table by investigative site for those who enter the trial.

Participant disposition will be summarized in a table by study period. Specifically, the table will include the number and percentage of participants who discontinued, and the number and percentage of participants by primary reason for discontinuation. This table will be completed in the Safety Population.

Additionally, a data listing will be generated that includes participant identification (ID), population type, and week of discontinuation.

4.3. Primary Endpoint Analysis

Efficacy analysis will be performed on the main analysis set and the sensitivity analysis set using a mixed-effect modeling strategy for repeated measures, described in Section 4.3.2. Raw CGM data will be used and derived in Analysis Data Model (ADaM) datasets to obtain the endpoints.

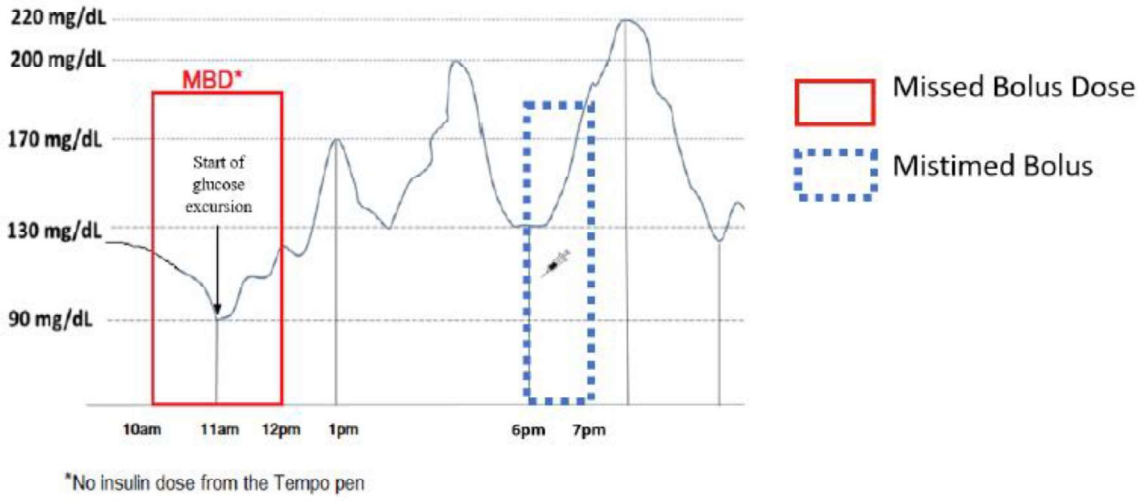
4.3.1. Definition of Endpoints

4.3.1.1. Missed Bolus Doses

MBDs will be identified by using the CGM (interstitial glucose values) and Tempo Smart Button data.

MBD is defined as no insulin dose from 1 hour prior to through 1 hour after the start of a glucose excursion, where a glucose excursion is defined as a >70 mg/dL (>3.9 mmol/L) rise within 2

hours, not preceded by a value <70 mg/dL (<3.9 mmol/L) (Edwards et al. 2022). If a dose between 1000 and 1100 hours would be classified as the correct or optimum time to administer the insulin dose before the 1100 hour meal, no insulin dose between 1000 and 1200 hours would be an MBD (Figure 4.1).



Abbreviation: MBD = missed bolus dose.

Figure 4.1. Missed bolus dose.

The Algorithm for identifying MBDs for each participant is as follows. Note that the algorithm will be applied to determine its adequacy, no adjustment of the algorithm will be made after the database lock.

1. Identify all the nadirs (Nt, t = 1, to m, m = the count of the last nadir) in the analysis period. The missed dose identification procedure starts from t = 1.
2. Identify missing doses associated with the nadirs:
   i. If an increase of 70 mg/dL or more from Nt is NOT found prior or at minimum (Nt + 2 hours, Nt+1), then move to the next nadir and repeat Step 2 (no excursion occurred post Nt and prior to next nadir or Nt + 2 hours, whichever is closer to Nt),
   ii. If an increase of 70 mg/dL or more from Nt is found prior or at minimum (Nt + 2 hours, Nt+1), then Pen data will be examined.
      a) If there is an injection within 1 hour prior to Nt, then move to the next nadir and repeat step 2,
      b) If there is NO injection found within 1 hour prior to Nt, and if the 70 mg/dL increase is prior to an injection after the Nt, or if there is an injection before reaching the 70 mg/dL increase but over 30 minutes after the Nt, then the number of missed dose + 1 and move to the next nadir and repeat Step 2,
3. Step 2 will be repeated until the end of the analysis period.

The definitions and clarification of the terms used in the algorithm:

1. **Nadir**: a nadir is defined as the time-point (Nt) with the lowest glucose in the time window from Nt – 30 minutes to Nt + 30 minutes, inclusive (in other words, 30 minutes prior to the time-point to 30 minutes post the time-point). The first and the last nadir in the analysis period might have fewer readings prior or post the nadir respectively. The nadir must not be preceded by a hypoglycemia (<70 mg/dL) (Figure 4.2).

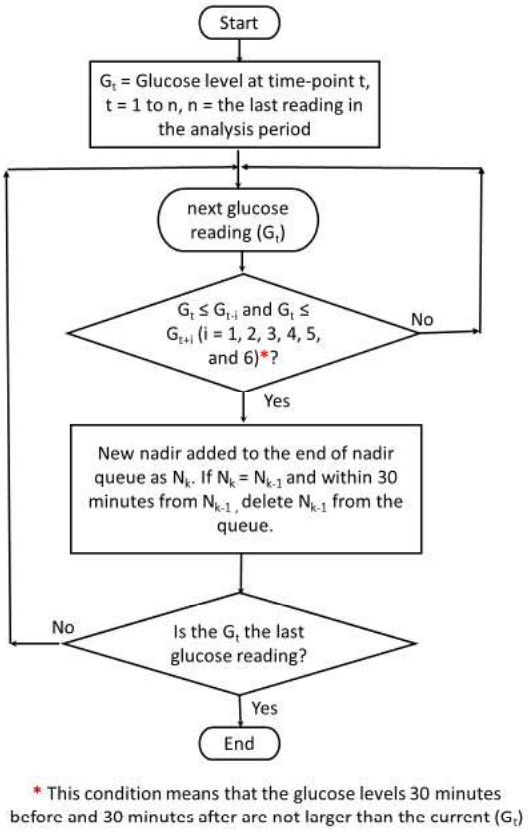
   If there are 2 or more tied nadirs identified within 30 minutes, the last nadir will be the nadir in the time window.

2. **Date and time of injection**: among the several records (within seconds or minutes, but not more than 30 minutes) captured for each injection in the Pen data, the date and time of the last record will be used for the injection in the calculation.

3. **Analysis period:** the period with consecutive CGM readings (every 5 minutes) without more than 2 hours gap.

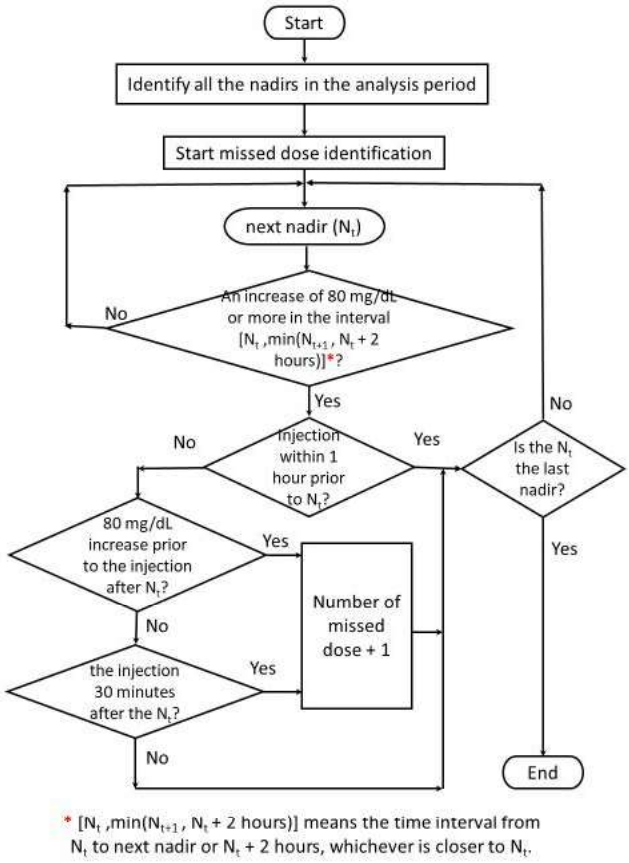
   If the gap is more than 2 hours, a new analysis period will start from the first reading post the gap to the next gap/end of the study period. The identification will be performed in the analysis period if the duration of the analysis period is more than 2 hours, but will not be done otherwise.

4. Algorithm will be applied in the analysis period based on available data, without missing data imputation (in other words, the time-points with missing data will not be taken into account). However, the values of "High" and "Low" will be replaced by 401 and 39 respectively, since the CGM platform cannot provide the actual results once the glucose levels are over 400 or under 40. Any value above 400 will be reset to 401 and any value under 40 will be reset to 39 if there are any such readings.



* The check for increase in the diagram would be of 70 mg/dL.

Figure 4.2. Nadir identification diagram.



* The check for increase in the diagram would be of 70 mg/dL.

Figure 4.3. Missed bolus dose identification diagram.

Based on the results of the missed bolus doses, the number of days per week with a missed bolus dose for each participant will be estimated.

For each participant the number of missed bolus doses per week in the period will be calculated using the formula:

*(Total number of Missed Bolus doses / Number of Days with Evaluable CGM data) * 7*

4.3.2. Main Analytical Approach

The primary endpoint is the difference in the average number of MBDs per week during the Study Period 2 (Weeks 15 to 18), compared to the Study Period 1 (Weeks 5 and 6). The average of the Week 5 average number of MBDs and Week 6 average number of MBDs will be considered baseline. The change for each of average number of MBDs of each Week 15, Week 16, Week 17, and Week 18 will then be calculated from the averaged baseline. MBD is defined as no insulin dose from 1 hour prior to through 1 hour after the start of a glucose excursion, where a glucose excursion is defined as a >70 mg/dL (>3.9 mmol/L) rise within 2 hours, not preceded by a value <70 mg/dL (<3.9 mmol/L).

The average MBDs per week will be calculated for:

- Weeks 5 and 6 for Study Period 1 (masked), and
- Weeks 15 to 18 for Study Period 2 (unmasked).

The actual MBDs and change from baseline will be summarized descriptively by study period and by week, and presented in a table.

The analyses for the primary endpoint will be conducted using a mixed-effect models for repeated measures (MMRM) using average MBD of each week (Weeks 5–6 and Weeks 15–18). The study period will be a fixed effect, baseline body mass index (BMI) and baseline HbA1c as covariates, and subject as the random effect. The repeated measure will be time, as measured in weeks (2 weeks in Study Period 1 and 4 weeks in Study Period 2 for each participant). The primary analysis will occur in the main analysis set and repeated in the sensitivity analysis set.

The MMRM model will be programmed using proc mixed in SAS Software version 9.4. The details of the model, specifically the chosen covariance structure, is subject to change based on findings during model building in SAS Software version 9.4. An unstructured covariance structure will be used to model the within-participant errors. If this structure fails to converge, the following covariance structures will be used in order until one converges:

- Toeplitz with heterogeneity
- autoregressive with heterogeneity
- compound symmetry with heterogeneous variances
- Toeplitz
- autoregressive, and
- compound symmetry without heterogeneous variances.

An example data structure excerpt regarding the primary efficacy endpoint for a hypothetical Subject 1 will be similar to Table 4.1.

Table 4.1. Data Structure Example

Usubjid	Week	StudyPeriod	BaseBMI	BaseHbA1c	Weekly Average MBD	Baseline MBD	Change in MBD
1	Week 5	Study Period 1	28.5	7.2	10.3	(10.3+9.6)/2=9.95	
1	Week 6	Study Period 1	28.5	7.2	9.6		
1	Week 15	Study Period 2	28.5	7.2	10.1	9.95	0.15
1	Week 16	Study Period 2	28.5	7.2	8.2	9.95	1.75

Usubjid	Week	StudyPeriod	BaseBMI	BaseHbA1c	Weekly Average MBD	Baseline MBD	Change in MBD
1	Week 17	Study Period 2	28.5	7.2	7.6	9.95	2.35
1	Week 18	Study Period 2	28.5	7.2	5.2	9.95	4.75

Abbreviations: BaseBMI = baseline body mass index; BaseHbA1c = baseline glycated hemoglobin; MBD = missed bolus dose; Usubjid = unique subject identification.

Based on the data structure above, example SAS Software version 9.4 program code for the MMRM is as follows:

```
proc mixed data = <data>;
      Class StudyPeriod week usubjid;
      Model Weekly_Average_MBD = StudyPeriod BaseBMI BaseHbA1c week/
      ddfm = kenwordroger;
      Random usubjid / subject = usubjid;
      Repeated Week/ subject = usubjid type = un rcorr;
      Lsmeans StudyPeriod/diff cl pdiff;
run;
```

In this MMRM, the model statement contains the outcome, the fixed effect (study period), and the covariates (baseline BMI and baseline HbA1c). The option ddfm specifies the method for computing the denominator degrees of freedom. The repeated statement handles the effect of time (there will be 1 measurement in Study Period 1 and 4 measurements in Study Period 2 for each participant) and options specify both the subject ID variable as well as the type of covariance structure that will be used. The LSMeans statement will output the model-adjusted least square means for each study period (masked and unmasked). The difference estimate of the least square means between Study Period 2 and Study Period 1, along with 2-sided 95% Confidence Interval (CI) and the p-value will also be estimated and reported.

4.3.3. Sensitivity Analysis

4.3.3.1. Varying Definitions of Missed Bolus Dose

Sensitivity analysis will be performed for the primary endpoint on the sensitivity analysis set. Varying definitions of MBD will be conducted as sensitivity analyses using a mixed-effect models for repeated measures as described in Section 4.3.2. The analyses will be completed in the sensitivity analysis set.

These include:

- MBD interval definition: 2 hours prior and 2 hours after start of glucose excursion (-2, 2), and
- MBD glucose excursion: ≥80 mg/dL (>4.4 mmol/L) rise within 2 hours.

4.3.4. Supplementary Analyses

A separate table will be produced after excluding baseline BMI from the covariate. The rest of the model and analysis will remain the same as the primary endpoint analysis.

4.4. Secondary Endpoints Analysis

The following secondary endpoints will be analyzed following the MMRM model for the masked and unmasked periods, unless otherwise noted. Baseline will be an average of the average of Week 5 and average of Week 6 (Study Period 1). Change from baseline will be calculated for Week 15, Week 16, Week 17, and Week 18 (Study Period 2). All analyses will be completed in the main analysis set. Analyses will be listed in mg/dL, participants will collect and transfer data in mmol/L, and necessary conversions will be performed in the study data tabulation models (SDTMs), ADaMs, and tables, listings, and figures (TLFs).

4.4.1. Secondary Endpoints

4.4.1.1. Main Analytical Approach

4.4.1.1.1. Continuous Glucose Monitoring Time In Range (≥70 to >180 mg/dL) in the Masked Versus Unmasked Portions of the Study

CGM percent of time in range (≥70 and ≤180 mg/dL) and change from baseline will be summarized descriptively by study period and by week, presented in a table. Actual values from Study Period 1 and Study Period 2 will be analyzed using an MMRM. Example SAS Software version 9.4 program code for the MMRM is as follows:

```
proc mixed data = <data>;
     Class StudyPeriod usubjid week;
     Model TIR = StudyPeriod BaseBMI BaseHbA1c week/ddfm=
kenwordroger;
     Random Usubjid / subject = usubjid;
     Repeated week/ subject = usubjid type = un rcorr;
     Lsmeans StudyPeriod/diff cl pdiff;
run;
```

4.4.1.1.2. Continuous Glucose Monitoring Time Above Range (>180 mg/dL) in the Masked Versus Unmasked Portions of the Study

CGM percent of time above range (>180 mg/dL) and change from baseline will be summarized descriptively by study period and by week, presented in a table. Actual values from Study Period 1 and Study Period 2 will be analyzed using an MMRM. The setup of the data will be the

same as in Section 4.3.2. Example SAS Software version 9.4 program code for the MMRM is as follows:

```
proc mixed data = <data>;
      Class StudyPeriod usubjid week;
      Model TAR= StudyPeriod BaseBMI BaseHbA1c week/ ddfm
=kenwordroger;
      Random Usubjid / subject = usubjid;
      Repeated week/ subject = usubjid type = un rcorr;
      Lsmeans StudyPeriod/diff cl pdiff;
run;
```

4.4.1.1.3. Continuous Glucose Monitoring Time Above Range (>250 mg/dL) in the Masked Versus Unmasked Portions of the Study

CGM percent of time above range (>250 mg/dL) and change from baseline will be summarized descriptively by study period and by week, presented in a table. Actual values from Study Period 1 and Study Period 2 will be analyzed using an MMRM. The setup of the data will be the same as in Section 4.3.2. Example SAS Software version 9.4 program code for the MMRM is as follows:

```
proc mixed data = <data>;
      Class StudyPeriod usubjid week;
      Model TAR = StudyPeriod BaseBMI BaseHbA1c week/ ddfm
=kenwordroger;
      Random Usubjid / subject = usubjid;
      Repeated week/ subject = usubjid type = un rcorr;
      Lsmeans StudyPeriod/diff cl pdiff;
run;
```

4.4.1.1.4. Continuous Glucose Monitoring Time Below Range (54 mg/dL ≤ TBR ≤ 70 mg/dL and < 54 mg/dL) in the Masked Versus Unmasked Portions of the Study

CGM percent of time below range (<70 mg/dL and < 54mg/dL) and change from baseline will be summarized descriptively by study period and by week, presented in a table. Actual values from Study Period 1 and Study Period 2 will be analyzed. The setup of the data will be the same as in Section 4.3.2. Example SAS Software version 9.4 program code for the MMRM is as follows:

```
proc mixed data = <data>;
      Class StudyPeriod usubjid week;
      Model TBR = StudyPeriod BaseBMI BaseHbA1c week/ ddfm
=kenwordroger;
      Random usubjid / subject = usubjid;
      Repeated week / subject = usubjid type = un rcorr
```

```
      Lsmeans StudyPeriod/diff cl pdiff;
run;
```

4.4.1.1.5. Coefficient of Variation and Mean Sensor Glucose from Continuous Glucose Monitoring Data

Coefficient of variation (CV) will be summarized descriptively by study period and by week, presented in a table. In addition, mean sensor glucose will be collected. Actual values and change from Study Period 1 to Study Period 2 will be analyzed using an MMRM. Example SAS Software version 9.4 program code for the MMRM is as follows:

```
proc mixed data = <data>;
      Class StudyPeriod usubjid week;
      Model CV = StudyPeriod BaseBMI BaseHbA1c week / ddfm =
      kenwordroger;
      Random usubjid / subject = usubjid;
      Repeated week / subject = usubjid type = un rcorr;
      Lsmeans StudyPeriod/diff cl pdiff;
run;
```

In addition, mean sensor glucose will be collected and MMRM will be generated as follows:

```
proc mixed data = <data>;
      Class StudyPeriod usubjid week;
      Model mean_glucose = StudyPeriod BaseBMI BaseHbA1c week / ddfm =
      kenwordroger;
      Random usubjid / subject = usubjid;
      Repeated week / subject = usubjid type = un rcorr;
      Lsmeans StudyPeriod/diff cl pdiff;
run;
```

4.4.1.1.6. Occurrence and Change in Mistimed Bolus Doses Frequency

Mistimed bolus dose is defined as administering a bolus dose from the start of a glucose excursion to 1 hour after the start of glucose excursion and before the peak of the glucose excursion. From the plot (Figure 4.1) in Section 4.3.1, if the correct or optimum time to administer a premeal insulin dose is between 1700 and 1800 hours, then an insulin dose between 1800 and 1900 hours will be considered a mistimed bolus dose. Mistimed bolus dose will be calculated and summarized in a table. The definition of a glucose excursion remains the same for an MBD and mistimed bolus dose.

Actual values and change in mistimed boluses doses will be summarized descriptively in a table for each study period and for each week as well. The average value of Weeks 5 and 6 will be used for baseline. Similar statistical analysis will be performed as MBD:

```
proc mixed data = <data>;
      Class StudyPeriod usubjid week;
      Model average_mistimed_bolus_dose = StudyPeriod BaseBMI BaseHbA1c
      week / ddfm = kenwordroger;
      Random usubjid / subject = usubjid;
      Repeated week / subject = usubjid type = un rcorr;
      Lsmeans StudyPeriod/diff cl pdiff;
run;
```

4.4.1.1.7. Total Insulin Dose per Day, Basal Dose, and Insulin Dose per Type of Meal

The change in insulin doses: basal and mealtime, ratio basal/mealtime, dose per meal as well and total dose in IU/kg, will be calculated and summarized descriptively in a table.

The type of meal will be defined by time intervals: breakfast (0600–1000 hours), lunch (1200–1500 hours), and dinner (1900—2200 hours).

Example SAS Software version 9.4 program code for the MMRM model is as follows:

```
proc mixed data = <data>;
      Class StudyPeriod usubjid week;
      Model Aval = StudyPeriod BaseBMI BaseHbA1c week/ ddfm =
      kenwordroger;
      Random usubjid / subject = usubjid;
      Repeated week/ subject = usubjid type = un rcorr;
      Lsmeans StudyPeriod/diff cl pdiff;
run;
```

4.4.1.1.8. Occurrence and Change in Correction Boluses

Correction boluses are defined as taking a bolus dose after the peak of a glucose excursion but within 4 hours from the start of a glucose excursion and prior to start of next glucose excursion.

Actual values and change in correction boluses will be summarized descriptively in a table. Similar statistical analysis will be performed as MBD:

```
proc mixed data = <data>;
      Class StudyPeriod usubjid week;
      Model correction_bolus = StudyPeriod BaseBMI BaseHbA1c week /
      ddfm = kenwordroger;
      Random usubjid / subject = usubjid;
      Repeated week/ subject = usubjid type = un rcorr;
```

```
      Lsmeans StudyPeriod/diff cl pdiff;
run;
```

4.4.1.1.9. Continuous Glucose Monitoring Curves

The MBD and mistimed bolus dose will be calculated using CGM plots and algorithm explained in Section 4.3.1.1. The association between MBD and mistimed bolus doses with time in range (TIR), time above range (TAR), time below range (TBR), and HbA1c will be analyzed using Spearman rank order correlation.

4.4.1.1.10. Participant and Healthcare Professional Questionnaires

Each question from participant and HCP questionnaires will be summarized in a table using frequency and percentages. Participant questionnaire summaries at Visits 1 (baseline) and Visit 3 (end of Study Period 1) from Study Period 1 will be compared to summaries at Visit 7 from Study Period 2 using shift tables. HCP questionnaire summaries will compare initial to end of study. No formal statistical testing is planned.

4.5. Exploratory Endpoints Analysis

4.5.1. Summary Statistics of Actual and Change in HbA1c

Actual HbA1c values at baseline (Visit 1) and Visit 7 and change from baseline will be presented in a table using descriptive continuous statistics. In addition, an MMRM will be run on this data. Example SAS Software version 9.4 program code for the MMRM is as follows:

```
proc mixed data = <data>;
      Class StudyPeriod usubjid week;
      Model HbA1c_change = StudyPeriod BaseBMI BaseHbA1c week/ ddfm =
      kenwordroger;
      Random usubjid / subject = usubjid;
      Repeated week/ subject = usubjid type = un rcorr;
      Lsmeans StudyPeriod/diff cl pdiff;
run;
```

4.5.2. Outcome of Study IORW Healthcare Professional Questionnaires

Responses from HCP questionnaires from initiation and end of study will be summarized.

4.5.3. Outcome of Study IORW Participant Questionnaires

Responses from participant questionnaires from Visits 1 (baseline), Visit 3 (end of Study Period 1), and Visit 7 (end of study) will be summarized using shift tables. CCI [redacted]

4.5.4. Continuous Glucose Monitoring Curves Integrated with Data Received from the Tempo Pen/Smart Button

The MBD and mistimed bolus dose will be calculated using CGM plots and algorithm explained in Section 4.3.1.1. The association between MBD and mistimed bolus doses with TIR, TAR, TBR and HbA1c will be analyzed using the Spearman rank order correlation. This analysis will be done on the sensitivity analysis set.

4.5.5. Glooko Research Mobile Application Use Data

Glooko mobile application data including the number of connections to the application, number of uploads from CGM, number of CCI data uploads, percentage of CGM data available, number of insulin data available, and number of prime before injection will be summarized in a table by study period.

4.5.6. Summary of Continuous Glucose Monitoring Wear Time

Summary of CGM wear time will be presented in a table by study period and correlated with MBD data.

4.5.7. Hypoglycaemia Fear Survey – Short Form Questionnaire Score

Hypoglycaemia Fear Survey – Short Form (HFS-SF) Questionnaire score will be summarized at Visit 1 and Visit 7 and change will be calculated. Scores will be analyzed with MBD data using Spearman correlation.

4.5.8. Summary Statistics for Daytime and Nighttime Continuous Glucose Monitoring Profiles

Summary of daytime CGM profiles and summary of nighttime (0000 to 0600 hours) CGM profiles for Study Period 1 and Study Period 2.

4.6. Other Safety Analyses

Analyses of AEs will be descriptive and include all data collected during the treatment period. All AEs will be coded using the standardized Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, version 24.1 or greater. Safety analysis and all analyses of adverse events will be carried out on the safety population.

4.6.1. Adverse Events

A table summary and listing and of all AEs will be generated which includes participant ID, System Organ Class (SOC), Preferred Term (PT), AE start date and study day, AE end date and study day, severity of AEs, seriousness of AEs, AE relatedness, action taken, and AE outcome. Additionally, a listing and table summary of unanticipated adverse device effects (UADEs) will be provided.

A separate table will be generated by SOC and PT for all the AEs. It will be represented in decreasing order of frequency by SOC and PT.

Serious adverse events

A table summary and listing of all serious adverse events (SAEs) will be generated which includes participant ID, SOC, PT, AE start date and study day, AE end date and study day, severity of AEs, AE relatedness, action taken, AE outcome, and SAE criteria.

Adverse events reported as reason for discontinuation from study

A table summary and listing of all AEs reported as reason for discontinuation will be generated which includes participant ID, SOC, PT, AE start date and study day, AE end date and study day, severity of AEs, seriousness of AEs, AE relatedness, action taken, and AE outcome.

Unanticipated adverse device events

A UADE is a serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of the participant.

A listing and table summary of UADEs will be provided.

4.6.2. Narratives

The following are "notable" events, from start of study intervention through end of study participation (or data cutoff for the submission if earlier):

- deaths
- SAEs, and
- permanent discontinuations of study intervention due to AEs.

Narratives (participant-level data and summary paragraph) will be provided for participants in the safety population with at least 1 notable event.

Safety topics of interest are not considered notable events, unless 1 of the above criteria is met. Displays with individual participant-level data will be created for safety topics of interest using various formats such as a customized listing and/or a customized graphical participant profile as specified in the section associated with the safety topic of interest. Medical case summaries or vignettes will be provided if deemed relevant for the discussion of the safety topic of interest.

4.6.3. Device Product Complaints

A listing of device deficiencies and device product complaints will be generated and the date, description of the device deficiency, and any associated AEs will be included, if applicable.

4.6.4. Hypoglycemic Events

The number of hypoglycemic events (CGM levels below the threshold for at least 15 minutes) will be summarized by study period in a table (Danne 2017). A data listing will also be generated. The number of Level 1 (≤70 mg/dL) and Level 2 (≤54 mg/dL) sensor detected hypoglycemic events will be summarized in a table, as well as participant-reported hypoglycemia if available.

Level 3 hypoglycemic events, which are considered as SAEs, will also be summarized and listed.

4.7. Vital Signs, Physical Findings, and Other Observations Related to Safety

4.7.1. Vital Signs and Physical Characteristics

Baseline vital signs (height, weight, and BMI calculated from height and weight) will be summarized in a table in the safety population.

Height, weight, and BMI changes from baseline at Visit 3 and Visit 7 will also be summarized.

A listing will be generated of any conditions recorded during the baseline physical examination.

4.8. Other Analyses

4.8.1. Other Sensitivity Analyses

Other sensitivity analyses that will be explored using descriptive analysis include the number of:

- weeks used in the analysis for the masked application period,
- days with CGM data in the unmasked application period, and
- participants that have dropped out during the unmasked application period.

4.8.2. Subgroup Analyses

Subgroup analysis will be performed on all participants for primary and secondary endpoints by the following factors:

- age group, and
- diagnosis (T1D or T2D).

Only summary statistics will be performed for all subgroups listed above.

4.9. Interim Analyses

No Interim Analysis will be performed.

5. Sample Size Determination

This clinical study aims to enroll approximately 50 participants (in other words, with signed informed consent and meeting all eligibility criteria) in sites across France. This sample size provides ≥80% power to detect a mean difference of daily MBD of 0.323 between the unmasked and masked RMA periods.

The sample size also assumes:

- a conservative correlation estimate of 0.2 between the unmasked and masked RMA periods
- an SD of 0.419 for the mean difference, and
- a 2-sided alpha of <0.05 (Adolfsson et al. 2020).

The estimated mean difference of 0.323 daily MBD is equivalent to a clinically relevant improvement of approximately 2.3 fewer MBD per week in the unmasked RMA period compared to the masked RMA period (also approximately 11% improvement).

A sample size of approximately 50 participants will be sufficient to allow:

- at least 24 participants will complete the study with analyzable data
- scope for increased variability (up to SD of 0.5)
- for non-analyzable participants due to technical problems, and
- 35% dropout rate is assumed based on previous study results (Adolfsson et al. 2020; Gomez-Peralta et al. 2023) and the impact of missing CGM data which will reduce the number of evaluable participants.

Participants who are entered but who do not proceed to the unmasked stage will be discontinued from the final efficacy analysis and may be replaced to ensure that enough participants complete the study. Best effort will be made to recruit an approximate ratio of 4:1 for T1D and T2D (approximately 40 participants with T1D and 10 participants with T2D) in this clinical study.

Withdrawals will be monitored to ensure there are enough participants with T2D enrolled.

6. Supporting Documentation

6.1. Appendix 1: Demographic and Baseline Characteristics

Demographics and other baseline characteristics will be analyzed on the safety population, unless otherwise specified in the subsections.

6.1.1. Demographics

Demographics and baseline characteristics will be presented in a table including age (in years), diabetes type, diabetes duration, gender, ethnicity, and baseline BMI and HbA1c.This table will be completed in the main analysis set, the sensitivity analysis set, and safety population. T1D and T2D participant's characteristics will be presented separately.

6.1.2. Concomitant Medications

Concomitant medications will be presented in a listing in the safety population. Additionally, a summary of glucose lowering concomitant therapy/insulin regimen will be completed in the safety population as well as specifically for participants with T2D.

6.1.3. Baseline Medical History

Medical history will be presented in a table in the safety population. A data listing will also be generated.

6.2. Appendix 2: Timing of Assessments and Events for Analysis

Study Day 1 is the date in which the participants start Visit 1. Study days will be calculated as follows:

Pre first usage, study days = event date – Visit 1 date

On the day of or post data upload, study days = event date –Visit 1 date + 1

The initial 4 weeks of the study will be used to allow participants to reach a routine before the baseline data assessment. Therefore, unless otherwise stated, data collected from the last 2 weeks of the masked period (Study Period 1, Weeks 5 and 6) will be used as baseline. Data from the last 4 weeks of the unmasked period (Study Period 2, Weeks 15 to 18) will be used for endpoint, in other words, 2 weeks prior to Visit 3 (face-to-face) and 4 weeks prior to Visit 7 (face-to-face) will be used. Data from these specified timepoints will be used to assess the primary and secondary objectives.

6.3. Appendix 3: Exposure to the GLOOKO Research Mobile Application

Amount of useable data from the CGM device and pen will be summarized for the main analysis set and presented in a table.

6.4. Appendix 4: Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements will include the following:

- summary of AEs, provided as a dataset which will be converted to an XML file, and
- SAEs and 'Other' non-SAEs summarized by treatment group and MedDRA PT.

An AE is considered 'Serious' whether or not it occurred after study Day 1.

An AE is considered in the 'Other' category if it occurred after study Day 1 and is not serious. For each SAE and 'Other' AE, for each term, the following are provided:

- the number of participants at risk of an event
- the number of participants who experienced each event term, and
- the number of events experienced.

For each SAE, these additional terms are provided for EudraCT:

- the total number of occurrences causally related to treatment
- the total number of deaths, and
- the total number of deaths causally related to treatment.

Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of participants in every treatment group may be excluded if a 5% threshold is chosen. Allowable thresholds include 0% (all events), 1%, 2%, 3%, 4%, and 5%.

AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

A demographic table including the following age ranges is required by EudraCT:

- in utero
- preterm newborn infants (gestational age <37 weeks)
- newborns (0–27 days)
- infants and toddlers (28 days–23 months)
- children (2–11 years)
- adolescents (12–17 years)
- adults (18–64 years)
- 65–84 years, and
- 85 years and over.

This study will include adults (18–64 years).

6.5. Appendix 5: Protocol Deviations

All protocol deviations will be summarized in a table. Major protocol deviations are defined as deviations that affect the outcome and/or impact any key endpoints and will be categorized by the sponsor prior to analysis. Major and minor protocol deviations will be summarized separately in tables for the safety population. Additionally, corresponding data listings will be generated.

7. References

Adolfsson P, Hartvig NV, Kaas A, et al. Increased time in range and fewer missed bolus injections after introduction of a smart connected insulin pen. *Diabetes Technol Ther*. 2020;22(10):709-718. https://doi: 10.1089/dia.2019.0411Battelino T, Alexander CM, Amiel SA, et al. Continuous glucose monitoring and metrics for clinical trials: an international consensus statement. *Lancet Diabetes Endocrinol*. 2023;11(1):42-57. https://doi.org/10.1016/S2213-8587(22)00319-9

Danne T, Nimri R, Battelino T, et al. International consensus on use of continuous glucose monitoring. *Diabetes Care*. 2017;40(12):1631-1640. https://doi.org/10.2337/dc17-1600

Edwards S, He X, Wang W, et al. Use of connected pen as a diagnostic tool to evaluate missed bolus dosing behavior in people with type 1 and type 2 diabetes. *Diabetes Technol Ther*. 2022;24(1):61-66. https://doi.org/10.1089/dia.2021.0239

Gomez-Peralta F, Abreu C, Fernández-Rubio E, et al. Efficacy of a connected insulin pen cap in people with noncontrolled type 1 diabetes: a multicenter randomized clinical trial. *Diabetes Care.* 2023; 46(1):206-208. https://doi.org/10.2337/dc22-0525

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