Protocol F3Z-MC-IOQV(a)

An Objective Assessment of Mealtime Bolus Insulin Behavior and Associated Factors

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Clinical Investigation Using the Reusable Insulin Injection Pen (LY8888AT)

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Protocol Electronically Signed and Approved by Lilly on date provided below.

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1. Synopsis

Title of Study:

An Objective Assessment of Mealtime Bolus Insulin Behavior and Associated Factors

Rationale:

Current diabetes management using basal/bolus insulin regimens requires a high level of patient engagement. One-third of patients with type 1 diabetes (T1D) or type 2 diabetes (T2D) reported insulin omission/nonadherence at least once in the past month. Of those patients, there was an average of 3.3 days per month of insulin omission/nonadherence (Peyrot et al. 2012). Patients often cite being too busy, fear of hypoglycemia, and concerns about weight gain as reasons for missing doses (Peyrot et al. 2012). Downloaded dosage data from insulin pump users indicated that 65% of pump-using children/adolescents with T1D missed 1 or more mealtime insulin bolus doses per week, with an association between missed bolus doses and glycated hemoglobin (HbA1c) results (Burdick et al. 2004). Prior to the development of insulin injection pens that track dose data, missed dosage data for multiple daily injection users was obtained by patient survey results only. The reusable insulin injection pen that records doses affords the opportunity to objectively gather omitted or suboptimal insulin dose data via pen download. Additionally, the use of continuous glucose monitoring (CGM) allows an assessment of the impact of bolus dosing on short-term glycemic control.

Objective(s)/Endpoints:

Objectives	Endpoint(s)
Primary	
• To objectively estimate the average number of days per month with a missed bolus dose in subjects with type 1 or type 2 diabetes with blinded CGM	• The average number of days per month with a missed bolus dose
Secondary	
• To estimate the average number of days per month with a missed bolus dose in subjects with type 1 or type 2 diabetes with unblinded CGM	• The average number of days per month with a missed bolus dose

• To estimate the percent time-in-range in subjects with type 1 or type 2 diabetes with
    o Blinded CGM
    o Unblinded CGM
	• Percent time-in-range (glucose >70 and ≤180 mg/dL)

• To estimate the percent of missed bolus doses in subjects with type 1 or type 2 diabetes with
    o Blinded CGM
    o Unblinded CGM
	• Percent of missed bolus doses per month

• To estimate the average number of missed bolus doses per day in subjects with type 1 or type 2 diabetes with
    o Blinded CGM
    o Unblinded CGM
	• Average number of missed bolus doses per day

• To estimate the Missed and Suboptimal Bolus Dose (MSBD) in subjects with type 1 or type 2 diabetes with
    o Blinded CGM
    o Unblinded CGM
	• The average number of MSBD events per month

Exploratory

• To assess the association between MSBD rate and CGM alert settings	• Correlation between MSBD rate and CGM alert settings
• To evaluate characteristics associated with short-term glycemic control in subjects with type 1 or type 2 diabetes	• Outcome for each PRO instrument*

• To estimate the average number of days per month with a missed bolus dose in subjects with type 1 diabetes with
  ○ Blinded CGM
  ○ Unblinded CGM
	• The average number of days per month with a missed bolus dose

• To estimate the average number of days per month with a missed bolus dose in subjects with type 2 diabetes with
  ○ Blinded CGM
  ○ Unblinded CGM
	• The average number of days per month with a missed bolus dose

Abbreviations: CGM = continuous glucose monitoring; PRO = patient-reported outcomes.

* if available for use

Summary of Study Design:

Study F3Z-MC-IOQV (IOQV) is a 12-week, multicenter, single-arm, outpatient, exploratory study with 2 study periods in subjects with T1D or T2D, respectively, using an investigational reusable insulin injection pen and a commercially available CGM device. Subjects participating in the study will follow an appropriate prescribed bolus insulin regimen suitable for their disease state using insulin lispro 100 units/mL injected via the reusable insulin injection pen. During the study, subjects will have their glucose monitored via a commercially available CGM device, which will be blinded during Study Period 1 and unblinded during Study Period 2. The main purpose of the study is to estimate missed bolus insulin doses in subjects with T1D or T2D.

Treatment Arm and Duration:

Study IOQV is a 12-week study with a single treatment arm. All subjects will administer insulin lispro U-100 (100 units/mL) using the investigational reusable insulin injection pen. All subjects will use a commercially available CGM device during the study.

Number of Subjects:

Screened: 80 subjects
Enrolled: 68 subjects
Completed: 50 subjects

Statistical Analysis:

The primary objective of Study IOQV is to objectively measure missed bolus doses in subjects with T1D or T2D with blinded CGM. The primary endpoint is the average number of days per month with a missed bolus dose, which will be estimated along with the 95% confidence interval. Secondary analyses will estimate the average number of days per month with a missed bolus dose with unblinded CGM, the percent time in glucose range, the percent of missed bolus doses, and the missed and suboptimal bolus dose (MSBD) by blinded and unblinded CGM. Exploratory analyses will evaluate the correlation between MSBD and CGM alert settings; graphically explore subject characteristics associated with short-term glycemic control; estimate

the average number of days per month with a missed bolus dose by type of diabetes (T1D, T2D) and CGM (blinded, unblinded).

Given the exploratory nature of Study IOQV, the analyses will be primarily descriptive. These will include mean, standard deviation, minimum, median, and maximum for continuous variables, and frequency and percentage for categorical variables.

2. Schedule of Activities

Table IOQV.1. **Schedule of Activities**

Procedure Weeks from Enrollment	Study Period 1 Blinded CGM Screening/ Enrollment V1 0W	V2 3W	V3 6W	Study Period 2 Unblinded CGM V4 9W	End of Study V5 12W	Early D/C	Notes
Visit Window	N/A	3D	3D	3D	3D	N/A	Allowable deviation +/- days or weeks from scheduled visit.
Office or home visit	X	X	X	X	X	X	
Informed consent	X						
Inclusion and exclusion criteria	X						
Demography	X						
Height and weight	X						
Medical history	X						
Current medical conditions	X						Including baseline diabetes disease characteristics
Pregnancy test	X						
Prescribed insulin regimen	X						Currently prescribed basal and bolus insulin regimen
Concomitant medication review	X	X	X	X	X	X	
Enrollment	X						
HbA1c blood draw [a]	X		X		X	X	
Pen dispensing	X						Record pen identification for dispensed pens
Pen training and start pen	X						
Confirm pen operation		X	X	X	X		
Pen collection/return					X	X	
CGM and glucose meter training	X						
CGM and pen data download		X	X	X	X	X	
Adjust CGM alert settings				X			
Hypoglycemic Confidence Scale	X		X		X	X	
Adult Low Blood Sugar Survey	X		X		X	X	

	Study Period 1 Blinded CGM			Study Period 2 Unblinded CGM			
The Big Five Inventory	X						
Health Problem Solving Scale	X		X		X	X	
Pictorial Representation of Illness and Self Measure	X		X		X	X	
General Life Stress Scale	X		X		X	X	
AE and SAE review		X	X	X	X	X	
Product complaint review		X	X	X	X	X	

Abbreviations: AE = adverse event; CGM = continuous glucose monitoring; D = days; D/C = discontinuation; HbA1c = glycated hemoglobin; N/A = not applicable; SAE = serious adverse event; V = visit; W = week.

[a] HbA1c testing will be performed by local laboratories.

3. Introduction

3.1. Study Rationale

Current diabetes management using basal/bolus insulin regimens requires a high level of patient engagement. One-third of patients with type 1 diabetes (T1D) or type 2 diabetes (T2D) reported insulin omission/nonadherence at least once in the past month. Of those patients, there was an average of 3.3 days per month of insulin omission/nonadherence (Peyrot et al. 2012). Patients often cite being too busy, fear of hypoglycemia, and concerns about weight gain as reasons for missing doses (Peyrot et al. 2012). Downloaded dosage data from insulin pump users indicated that 65% of pump-using children/adolescents with T1D missed 1 or more mealtime insulin bolus doses per week, with an association between missed bolus doses and glycated hemoglobin (HbA1c) results (Burdick et al. 2004). Prior to the development of insulin injection pens that track dose data, missed dosage data for multiple daily injection users was obtained by patient survey results only. The investigational reusable insulin injection pen (hereafter referred to as "pen") affords the opportunity to objectively gather omitted or suboptimal insulin dose data via pen download. Additionally, the continuous glucose monitoring (CGM) allows an assessment of the impact of bolus dosing on short-term glycemic control.

Study F3Z-MC-IOQV (IOQV) is an exploratory study to objectively estimate the average number of days per month subjects have a missed bolus dose in subjects with T1D or T2D with blinded CGM. In addition, the study will explore any differences in missed bolus insulin doses by diabetes type, by CGM (blinded, unblinded), and by subject characteristics. Study IOQV will utilize data from the pen to obtain bolus dose data (including amount and time of dose), along with blinded and unblinded CGM to assess short-term glycemic control.

3.2. Background

Glycemic control is the ultimate goal of any diabetes treatment regimen. However, many subjects with T1D and T2D continue to have poor glycemic control in large part due to lower adherence to their prescribed diabetes treatment regimen due to reasons including diabetes knowledge, personal-perceived control, diabetes distress, and regimen-related distress, among others (Al-Qazaz et al. 2011; Cummings et al. 2014; Gonzalez et al. 2015). Many previous analyses have been performed by survey results and self-reporting. The pen, CGM, and patient-reported outcomes (PRO) data can document insulin dosing and blood glucose, and inform behavior concerning insulin dosing.

3.3. Benefit/Risk Assessment

More information about the known and expected benefits, risks, serious adverse events (SAEs), and reasonably anticipated adverse events (AEs) can be found in the insulin lispro 100 units/mL United States Package Insert (USPI), and pen Investigator's Brochure (IB).

4.   Objectives and Endpoints

Table IOQV.2 shows the objectives and endpoints of the study.

Table IOQV.2.   Objectives and Endpoints

Objectives	Endpoint(s)
Primary	
• To objectively estimate the average number of days per month with a missed bolus dose in subjects with type 1 or type 2 diabetes with blinded CGM	• The average number of days per month with a missed bolus dose
Secondary	
• To estimate the average number of days per month with a missed bolus dose in subjects with type 1 or type 2 diabetes with unblinded CGM	• The average number of days per month with a missed bolus dose

• To estimate the percent time-in-range in subjects with type 1 or type 2 diabetes with
  o   Blinded CGM
  o   Unblinded CGM
	• Percent time-in-range (glucose >70 and ≤180 mg/dL)

• To estimate the percent of missed bolus doses in subjects with type 1 or type 2 diabetes with
  o   Blinded CGM
  o   Unblinded CGM
	• Percent of missed bolus doses per month

• To estimate the average number of missed bolus doses per day in subjects with type 1 or type 2 diabetes with
  o   Blinded CGM
  o   Unblinded CGM
	• Average number of missed bolus doses per day

• To estimate the Missed and Suboptimal Bolus Dose (MSBD) in subjects with type 1 or type 2 diabetes with
  o   Blinded CGM
  o   Unblinded CGM
	• The average number of MSBD events per month

Exploratory	
• To assess the association between MSBD rate and CGM alert settings	• Correlation between MSBD rate and CGM alert settings
• To evaluate characteristics associated with short-term glycemic control in subjects with type 1 or type 2 diabetes	• Outcome for each PRO instrument*

• To estimate the average number of days per month with a missed bolus dose in subjects with type 1 diabetes with
  o   Blinded CGM
  o   Unblinded CGM
	• The average number of days per month with a missed bolus dose

• To estimate the average number of days per month with a missed bolus dose in subjects with type 2 diabetes with
  o   Blinded CGM
  o   Unblinded CGM
	• The average number of days per month with a missed bolus dose

Abbreviations: CGM = continuous glucose monitoring; PRO = patient-reported outcomes.

* if available for use

5. Study Design

5.1. Overall Design

Study IOQV is a 12-week, multicenter, single-arm, outpatient, exploratory study with 2 study periods in subjects with T1D or T2D. Study IOQV will use an investigational pen injector, which captures bolus insulin doses, and a commercially available CGM device. Subjects participating in the study will follow an appropriate prescribed insulin regimen suitable for their disease state using insulin lispro 100 units/mL injected via the pen. During the study, subjects will have their glucose monitored via the CGM device, which will be blinded during Study Period 1 and unblinded during Study Period 2. In addition, subjects will take PRO evaluations to assess potential behaviors related to short-term glycemic control.

Study governance considerations are described in detail in Appendix 2.

One study center will be managed by Sponsor designee CCI , using telemedicine, mobile study nurses, and an electronic application called CCI . Further details about management of this study center by CCI are provided in Appendix 4.

Figure IOQV.1 illustrates the study design.
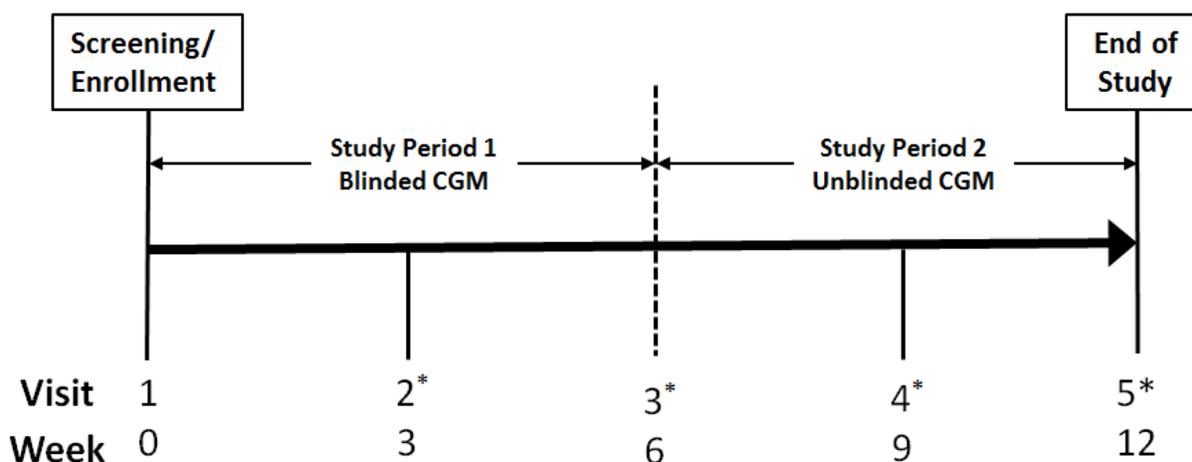
*Pen and Continuous Glucose monitor (CGM) Data collection
Note: All visits are in clinic/home

Figure IOQV.1.   Illustration of study design for Clinical Protocol F3Z-MC-IOQV.

5.1.1. Eligibility and Enrollment

Subjects will be screened at Visit 1 (Week 0) for the assessment of enrollment eligibility. Screening assessments are outlined in the Schedule of Activities (SOA) (Table IOQV.1). Patients who pass screening assessments based on the inclusion and exclusion criteria set forth in Sections 6.1 and 6.2 are eligible to be enrolled in the study.

5.1.2. Study Period 1

At Visit 1 (Week 0), informed consent will be obtained from each subject.

Each subject will have a unique subject number assigned, additional eligibility requirements evaluated, and laboratory tests will be performed as outlined in the SOA (Table IOQV.1). After confirming eligibility (Visit 1), subjects will be trained on the devices to be used in the study. Subjects will be trained by the study site to self-insert the CGM sensor. If the subject cannot self-insert the CGM sensor, the site/study personnel will insert the CGM sensor. Subjects will be blinded to their CGM data. Subjects will continue their routine blood glucose monitoring as needed while using the blinded CGM device. However, subjects must monitor their blood glucose at least twice per day using a provided glucose monitor to calibrate the CGM device (Section 7.1.2.1).

Subjects will begin using the pen to inject insulin lispro 100 units/mL and the blinded CGM device as directed at Visit 1 (Week 0) after training. Subjects entering the study taking rapid-acting insulin analog other than insulin lispro 100 units/mL should be switched to insulin lispro 100 units/mL using a 1:1 dose conversion unless there are safety concerns as identified by the investigator. Subjects should continue their prestudy basal insulin and concomitant anti-hyperglycemic therapy and the investigator may adjust the insulin and other diabetes therapy as needed. In addition, the blinded CGM device will record the subject's glucose during Study Period 1 as outlined in the SOA.

A training checklist for the pen and the CGM device will be provided to investigators to aid in subject training. This training includes, but is not limited to, the operation of the pen and CGM device, CGM device calibration, clearing CGM alerts, and other study procedures. Subjects may be retrained on the aforementioned items if deemed appropriate by the study site. See Section 7.1.2 for more information regarding the devices used in the study.

Subjects will be instructed to insert a new sensor weekly and recalibrate the CGM device throughout the study. At Visit 2 (Week 3) and Visit 3 (Week 6), subjects will have their blinded CGM data and pen data downloaded by the study site personnel.

5.1.3. Study Period 2

Following the completion of Visit 3 (Week 6) assessments, subjects will begin Study Period 2 and will be unblinded to their CGM data.

At Visit 4 (Week 9), subjects will have their unblinded CGM data and pen data downloaded by the study site personnel and any required adjustments to their CGM device alarms will be performed by the study site. Insulin adjustment recommendations will be provided by the investigator and designated staff based on the available glucose and insulin data. At Visit 5 (Week 12), subjects will complete their participation in the study, and the site will download all of the pen and CGM data since the last visit.

5.2.   Number of Subjects

Approximately 80 patients will be screened to achieve approximately 68 enrolled leading to approximately 50 evaluable subjects for Study IOQV. A minimum of 28 patients and a maximum of 40 patients each of T1D and T2D will be enrolled.

5.3.   End of Study Definition

End of the study is the date of the last visit shown in the SOA (Section 2) for the last subject.

5.4.   Scientific Rationale for Study Design

This exploratory study objectively estimates bolus doses and their relationship to short-term glycemic control and PROs. The pen allows for objective collection of data that can be assessed as missed or suboptimal doses. Prior to a downloadable pen, other investigators have collected bolus data for multiple daily injection users subjectively from patient and/or healthcare professional reports. There is no standard of care or comparator arm because the primary objective of this study is to objectively estimate missed bolus doses. Therefore, the second half of Study Period 1 (Visit 2 [Week 3] to Visit 3 [Week 6]) will be used for analyses with blinded CGM. The study duration of 12 weeks (2 parts of 6 weeks each) is adequate based on the inclusion criteria of 3 or more bolus doses daily for the assessment of missed bolus doses. Each enrolled subject must be on a mealtime bolus insulin regimen with each individual bolus insulin dose being <40 units (Section 6.1). Adult T1D and T2D populations were chosen to explore whether there might be differences based on disease type.

5.5.   Justification for Dose

The dose of insulin lispro 100 units/mL to be used in the study will be different for each subject according to their insulin needs. Subjects will be instructed to continue their prestudy basal insulin and concomitant antihyperglycemic therapy. The investigator can make basal and bolus insulin adjustments as needed. The prescribed insulin regimen will be determined from the subject's medical records at the start of the study, and any dosage adjustments needed during the study shall be documented for analysis (Section 7.4). Subject's basal insulin and concomitant antihyperglycemic therapy may be adjusted as needed per investigator's discretion as needed for safety (Section 7.7).

6. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

6.1. Inclusion Criteria

Patients are eligible to participate in the study only if they meet all of the following criteria at screening:

Type of Subject and Disease Characteristics

    [1]   Subjects with a T1D or T2D diagnosis:

        i)   Mealtime bolus dose insulin ($\geq$3 doses).

        ii) Each individual bolus insulin dose must be <40 units.

        iii) Subjects must be taking a stable insulin dose regimen per the investigator's judgement for the 3 months preceding screening.

    [2]   Subjects must be taking a bolus insulin analog (for example insulin lispro [U-100]/[U-200], insulin aspart, or insulin glulisine). In addition, the subject must be able to switch to insulin lispro U-100 for the duration of the trial per the investigator's judgement, if taking a bolus insulin analog other than insulin lispro U-100.

    [3]   Subjects must have a HbA1c $\geq$8.0% in the last 6 months.

    [4]   Subjects with T1D must be $\geq$21 to $\leq$65 years of age at screening. Subjects with T2D must be $\geq$35 to $\leq$65 years of age at screening.

Subject Characteristics

    [5a] <u>Male subjects:</u>

        No male contraception required except in compliance with specific local government study requirements.

    [5b] <u>Female subjects:</u>

        Women of non-childbearing and childbearing potential. Women of childbearing potential are defined as:

        Female subjects as any female who has experienced menarche and who is NOT permanently sterile or postmenopausal. Postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause. These subjects:

           I.   Must agree to use 1 highly effective method of contraception, or a combination of 2 effective methods of contraception for the entirety of the study (Appendix 3)

II.   Must test negative for pregnancy as indicated by a negative serum or urine pregnancy test at screening.

[6]   Subjects with prior CGM/flash glucose monitoring experience must have stopped CGM/flash glucose monitoring ≥3 months prior to enrollment.

[7]   Study materials and devices will only be provided in English. Subjects must be comfortable with understanding the English language.

Informed Consent

[8]   Are able and willing to give signed informed consent.

6.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria:

Medical Conditions

[9]   Subjects with known tape/adhesive allergies with CGM sensors.

[10]   Subjects with medical conditions, visual, physical, psychiatric, or cognitive impairment(s) that may preclude the ability to participate in the trial per the investigator's discretion.

[11]   Have a documented medical history of or obvious clinical signs or symptoms of liver disease, acute or chronic hepatitis, or a history of alanine aminotransferase or aspartate aminotransferase levels ≥3 times the upper limit of the reference range within the last 6 months before screening.

[12]   Have documented medical history of chronic kidney disease stage 4 and higher within the last 6 months before screening or history of renal transplantation.

[13]   Have active malignancy.

[14]   Are pregnant or planning to become pregnant.

[15]   Are on or are intending on beginning a weight loss program.

Prior/Concomitant Therapy

[16]   Subjects with T1D who have taken off-label antihyperglycemic agents within 3 months prior to screening.

[17]   Have received insulin by continuous subcutaneous insulin infusion in the 3 months prior to screening.

[18]   Subjects taking opioid medications at screening for medically invalid reasons or at doses considered excessive for the treated condition per the investigator's discretion.

[19]   Subjects on routine use of acetaminophen at screening per the investigator's judgement.

[20] Currently undergoing systemic treatment with:

- Immunosuppressive medication.

- Chronic (lasting longer than 2 weeks) systemic glucocorticoid therapy (excluding topical and inhaled preparations) or have received such therapy within 2 weeks immediately before Visit 1 (Week 0).

Prior/Concurrent Clinical Trial Experience

[21] Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

[22] Have participated, within the last 30 days, in a clinical study involving an investigational product. If the previous investigational product has a long half-life, 5 half-lives or 30 days (whichever is longer) should have passed.

[23] Have previously completed or withdrawn from this study.

Other Exclusions

[24] Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

[25] Are Lilly employees or are employees of any third party involved in the study who require exclusion of their employees.

[26] Are unwilling or unable to comply with the use of a data collection device to directly record data from the subject.

6.3. Lifestyle Restrictions

Subjects must have a stable lifestyle with no changes to dietary or exercise habits during the course of the study.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

7. Treatments

7.1. Treatments Administered

This study involves the treatment of subjects with diabetes with marketed insulin lispro (100 units/mL) administered by the pen. Table IOQV.3 shows the treatment regimens. Subjects will continue their pre-study concomitant anti-hyperglycemic medication and basal insulin therapies during the study.

Table IOQV.3.　　　　　　**Treatment Regimens**

Study Period 1	Study Period 2
Insulin lispro doses as prescribed delivered via the pen. CGM data blinded.	Insulin lispro doses as prescribed delivered via the pen. CGM data unblinded.

Abbreviation: CGM = continuous glucose monitoring.

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the pen, the commercially available CGM device, and the glucometer to the subject or the subject's legal representative.

- maintaining accurate records of all pens, medication vouchers/pharmacy cards, and device dispensing and collection.

- at the end of the study, all pens, the CGM device, and glucose meter must be returned to Lilly or its designee.

7.1.1. Packaging and Labeling

Clinical study materials will be labeled according to United States (US) regulatory requirements.

7.1.2. Medical Devices

The medical device provided for use in the study is the investigational reusable insulin injection pen, which collects dose administration information. The other devices provided for use during the study are a commercially available CGM device (CCI　　　　　　　 and a glucose meter.

As each subject completes the study, accountability will be completed and the returned items will be stored as instructed. Detailed information about this process will be available as part of site's working manual.

7.1.2.1. Continuous Glucose Monitoring

The commercially available CGM device that will be used during the study is the CCI ，which consists of a glucose sensor, data transmitter, and data receiver that assesses interstitial glucose readings every 5 minutes. The CCI can be blinded or unblinded. The CCI should be calibrated at least once every 12 hours by a finger stick blood glucose reading from the provided glucose meter. The calibration of the CCI should be done during both study periods when the CGM system is in use.

7.1.2.2. Investigational Reusable Insulin Injection Pen

The insulin injection device to be used in Study IOQV is an investigational reusable pen injector for the delivery of a subcutaneous injection of insulin using the standard Lilly 3 mL Humalog U-100 glass cartridges. The pen is a variable dose device for use in patients with T1D or T2D. The pen dials in 1-unit increments with a 60 unit maximum dose, and requires a new pen needle for each injection. The pen contains an organic light-emitting diode display and memory function which allows for insufficient remaining dose detection (while displaying the remaining partial dose), last dose display (time since last dose and units delivered), a full dose history in memory, and "Injection Complete" prompt. The pen contains electronics with the capability to store dosage data and download the data by the study site personnel. Due to the investigational nature of the reusable insulin injection pen, this study is also following 21 CFR 812 guidelines for investigational devices.

7.2. Method of Treatment Assignment

Subjects who meet all inclusion/exclusion criteria (Sections 6.1 and 6.2) will be enrolled into the study at Visit 1 (Week 0). This study is an open-label, single-arm study for which all subjects are receiving insulin lispro 100 units/mL.

7.2.1. Selection and Timing of Doses

The doses will be administered according to the subject's usual practices. The actual dose and time of all dose administrations will be recorded by the pen and downloaded by study site personnel. Subjects will continue their prestudy basal insulin and concomitant antihyperglycemic therapy and the investigator may make insulin dose adjustments as indicated.

7.3. Blinding

This is an open-label study. Subjects and study personnel will not be blinded to insulin lispro 100 units/mL administered via the pen. Subjects will not have access to their historical bolus dosing data from the pen with the exception of the display indicating the duration since their last bolus dose. Additionally during Study Period 1, subjects will be blinded to their CGM readings (Figure IOQV.1). Subjects and the study personnel will be unblinded to the subject's CGM data during Study Period 2.

7.4. Dosage Modification

Insulin dosage modifications are not required during the study but may be indicated. Therefore, insulin adjustments are allowed based on the investigator's medical judgement using the available glucose and insulin data. Subjects who are adjusted to a single bolus insulin dose of >40 units per injection will be discontinued from the study.

7.5. Preparation/Handling/Storage/Accountability

The investigator or his/her designee is responsible for the following:

- Device training on the pen, CGM system, and glucometer.

- Completion of the checklist for all device training.

- Ensuring that only subjects receive study treatment vouchers.

- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment voucher accountability, reconciliation, and record maintenance (such as receipt, reconciliation, and final disposition records).

7.6. Treatment Compliance

Compliance of pen utilization will be assessed at each visit. To avoid missing data, the pen and CGM data will be downloaded at predetermined time points described in the SOA.

7.7. Concomitant Therapy

Other concomitant therapies that are part of routine care are allowed and can be used during the study at the investigator's discretion. A list of medications not allowed will be provided separately. Any change in the list of medications not allowed will be communicated to investigators, and will not constitute a protocol amendment.

A subject's concomitant antihyperglycemic therapy may be adjusted as needed per investigator's discretion for safety.

7.8. Treatment after the End of the Study

7.8.1. Treatment after Study Completion

The pen or insulin lispro will not be made available to study participants after conclusion of the study. Subjects will resume their standard insulin therapy at the completion of the study.

8.   Discontinuation Criteria

8.1.   Discontinuation from Study Treatment

8.1.1. Permanent Discontinuation from Study Treatment

Discontinuation from study treatment (i.e., the pen) for a total of >3 days would lead to permanent discontinuation from study treatment as the purpose of the study is to collect data on bolus dosing. If a subject is permanently discontinued from study treatment, they will also be discontinued from the study.

8.1.2. Temporary Discontinuation from Study Treatment

Subjects may temporarily discontinue study treatment for a total of ≤3 days due to temporary hospitalization, medical procedure, loss of the pen, or per the investigator's judgement.

8.1.3. Discontinuation of Inadvertently Enrolled Subjects

If the sponsor or investigator identifies a subject who did not meet enrollment criteria and was inadvertently enrolled, then the subject should be permanently discontinued from study treatment. Safety follow-up is as outlined in the SOA (Table IOQV.1), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of the protocol.

8.2.   Discontinuation from the Study

Subjects will be discontinued in the following circumstances:

- if the subject becomes pregnant during the study as determined by a serum or urine pregnancy test performed at the investigator's suspicion of possible pregnancy.

- enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research as judged by the sponsor not to be scientifically or medically compatible with this study.

- for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).

- subjects who are adjusted to a single bolus insulin dose of >40 units per injection.

- if the subject discontinues study treatment for a total of >3 days.

- **Investigator Decision**

  o   the investigator decides that the subject should be discontinued from the study.

  o   if the investigator deems it necessary to stop insulin lispro treatment.

- **Subject Decision**

       ○ the subject or the subject's designee requests to be withdrawn from the study.

- **Sponsor Decision**
  - ○ if the subject loses or otherwise renders the pen (and its replacement pen) inoperable, the sponsor may discontinue that subject from the study.
  - ○ the sponsor decides to stop the study.

Subjects discontinuing from the study prematurely for any reason should complete AE and other safety follow-up per Section 2 (SOA), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.3. Lost to Follow-Up

A subject will be considered lost to follow-up if he or she repeatedly fails to attend scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact subjects who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

9. Study Assessments and Procedures

Section 2 lists the SOA, with the study procedures and their timing (including tolerance limits for timing).

9.1. Efficacy Assessments

9.1.1. Primary Efficacy Assessments

The primary efficacy assessment objectively estimates the average number of days per month with a missed bolus dose in subjects with type 1 or type 2 diabetes using blinded CGM measurements and the pen. Missed bolus doses will be determined by the glucose excursion as measured by the CGM.

- A subject is counted as missing 1 injection, if the subject does not have any injection record during the 1-hour interval prior to a glucose excursion (≥80 mg/dL) in the 2-hour postprandial interval.
  Example: In the theoretical CGM profile (Figure IOQV.2), 2 glucose excursions ≥80 mg/dL within a 2-hour interval are observed:
  o   nadir at 11 am and peak at 12 pm,
  o   nadir at 1:30 pm and high at 2:15 pm.

  If the associated insulin pen data show no injection between 10 am and 11 am and 1 injection between 12:30 pm and 1:30 pm, then the subject has 1 missed injection corresponding to the 11 am-12 pm glucose excursion.

Figure IOQV.2.   **Example of a missed injection using a CGM profile.**

9.1.2. Secondary Assessments

Study IOQV will have 5 secondary efficacy measures as described in Table IOQV.2. The first secondary objective is similar to the primary objective (Section 9.1.1) except that the information to be analyzed will be using unblinded CGM data. Missed bolus doses will be determined by the glucose excursion as measured by the unblinded CGM.

Study IOQV will also estimate the percent time-in-range in subjects with T1D or T2D using blinded and unblinded CGM data. The glucose range for this analysis is >70 and ≤180 mg/dL. In addition, the percent of missed bolus doses per month and the average number of missed bolus doses per day will be estimated in subjects with T1D and T2D on both the blinded and unblinded CGM. The final secondary objective will estimate the average number of MSBD events per month in subjects with T1D or T2D using data obtained from the blinded and unblinded CGM phases of the study.

9.1.3. Exploratory Assessments

Study IOQV will possibly explore 6 different PRO evaluations that the subject will perform at time points outlined in the SOA (Table IOQV.1). These PRO evaluations are the Hypoglycemic Confidence Scale (HCS), Adult Low Blood Sugar Survey (ALBSS), the Big Five Inventory (BFI), Health Problem Solving Scale (HPSS), the Pictorial Representation of Illness and Self Measure Revised II (PRISM R II), and the General Life Stress Scale (GLSS). The details of each PRO evaluation are listed in the following sections.

9.1.3.1. Hypoglycemic Confidence Scale

The HCS examines the degree to which people with diabetes feel able, secure, and comfortable regarding their ability to stay safe from hypoglycemic-related problems (Polonsky et al. 2017). The HCS has been validated for use in adults with T1D and insulin-using T2D patients. This evaluation uses the Likert scale with ratings of not confident at all, a little confident, moderately confident, and very confident to rate a subject's response to 9 items during the evaluation (8 items for subjects without a partner and 9 for subjects with a partner). Each item will receive a score from 1 to 4 based on the subject's response. Scores are calculated as the sum total item score divided by the number of items completed (8 items for participants without a partner and 9 for participants with a partner). Higher scores mean greater confidence (Polonsky et al. 2017).

9.1.3.2. Adult Low Blood Sugar Survey

The ALBSS is an evaluation of the fear of hypoglycemia derived from the widely used and validated ALBSS. This evaluation uses the Likert scale of 0 ("never") to 4 ("almost always") to rate 11 items (Behavior domain with 5 items; Worry domain with 6 items). A higher total score means greater fear (Cox et al. 1987; Grabman et al. 2017).

9.1.3.3. The Big Five Inventory

The BFI is 44-item inventory that measures an individual on the Big Five Factors (dimensions) of personality, Extraversion versus introversion (8 items), Agreeableness versus antagonism (9 items), Conscientiousness versus lack of direction (9 items), Neuroticism versus emotional stability (8 items), and Openness versus closedness to experience (10 items). Identifying a patient's thinking, feeling, and behaving may help clinicians avoid suggesting solutions that will not work for that patient's personality type (APA WWW). The evaluation uses a Likert scale of (1) disagree strongly, (2) disagree a little, (3) neither agree nor disagree, (4) agree a little, and (5) agree strongly. (Goldberg 1981).

9.1.3.4. Health Problem Solving Scale

Patient problem-solving has been shown to be a predictor of coping and health behaviors and was related to improved outcomes in diabetes (Glasgow et al. 2007). The HPSS can be used to "identify patients who may be most in need of problem-solving interventions as part of patient education and disease self-management training" (Hill-Briggs et al. 2007). It is of interest to evaluate a person's problem-solving abilities in association with the number of and/or frequency of missed mealtime insulin doses.

The scale is a set of 50 items that the subject rates using a 5-point Likert scale ranging from "not at all true of me" (0 points) to "extremely true of me" (4 points). Seven subscale scores are calculated by summing scores for each item in the respective subscale. The HPSS total score is derived by using the sums of the subscale averages, with reverse scoring of the negative subscales. Higher subscale scores indicate more of a problem-solving characteristic. A higher total HPSS score indicates a more effective health-related problem-solving skill (Hill-Briggs et al. 2007).

9.1.3.5. Pictorial Representation of Illness and Self Measure Revised II

The PRISM R II is a visual representation of burden of suffering from diabetes in a patient's life. This evaluation allows for discussion on the importance of diabetes in the patient's life that may provide insight into any barriers to successful diabetes management.

The PRISM R II consists of a large white paper circle, representing the subjects' life, with a yellow paper circle placed in the middle and in front/on top of the white circle, representing the respondents' self. Three differently sized red paper circles represent the respondents' diabetes. The diabetes circles are respectively smaller than, equal to, and larger than the self circle. Subjects are given the following written instruction: "The white circle represents your current life and the yellow circle represents you. The three red circles represent your diabetes. Select from the three red circles the one that, in your view, represents your diabetes most accurately. Place the circle into your life. Locate the circle at the place that the diabetes occupies in your life. You can place the circle anywhere in your life, also entirely or partially on top of your self." Two measures are extracted from the PRISM R II, Self Illness Separation where greater distances correspond to less burden and the Illness Perception Measure ranging from 1 to 3 with 1 representing the smallest disk (Klis et al. 2008).

9.1.3.6. General Life Stress Scale

The GLSS assesses the degree of stress an individual is currently experiencing in 5 general areas of life (finance, work, their romantic relationship, family, and health problems—modified to inquire about health problems other than diabetes) within 6 items, with response options ranging from 0 ("none") to 4 ("a great deal"). The total score is calculated, with higher scores reflecting greater overall life stress (Hessler et al. 2016).

9.1.4. Appropriateness of Assessments

The objective collection of bolus dosing data using the pen will help to better understand actual dosing behavior. The use of the commercially available CGM device will provide an assessment

of blood glucose control to better understand the relationship with bolus dosing. The PROs will allow a better understanding of patient's behavior and the relationship with bolus dosing.

9.2. Adverse Events and Device Complaints

Investigators are responsible for monitoring the safety of subjects who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject. The investigator is responsible for the appropriate medical care of subjects during the study. Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the subject to discontinue the investigational product before completing the study. The subject should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator. Lack of drug effect is not an AE in clinical studies.

Hypoglycemia, as outlined in Section 9.2.1.1, should be considered an AE when reported by the study participant.

After the informed consent form (ICF) is signed, study site personnel will record via the case report form (CRF) the occurrence and nature of each subject's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure, investigational device, or investigational product, via CRF.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, investigational study device, or a study procedure, taking into account the disease, concomitant treatment, or pathologies.

A "reasonable possibility" means that there is a cause and effect relationship between the investigational product, investigational study device and/or study procedure, and the AE.

The investigator answers yes/no when making this assessment. If relatedness to study device is "yes", a product complaint will also need to be submitted.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a subject's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via CRF, clarifying if possible, the circumstances leading to any dosage modifications, or discontinuations of treatment.

9.2.1. Serious Adverse Events

An SAE is any AE from this study that results in one of the following outcomes:

- death

- initial or prolonged subject hospitalization

- a life-threatening experience (i.e., immediate risk of dying)

- persistent or significant disability/incapacity

- congenital anomaly/birth defect

- important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse.

- when a condition related to the pen necessitates medical or surgical intervention to preclude either permanent impairment of a body function or permanent damage to a body structure, the serious outcome of "required intervention" will be assigned.

- severe hypoglycemia

All AEs occurring after signing the ICF are recorded in the CRF and assessed for serious criteria. The SAE reporting to the sponsor begins after the subject has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, the SAE should be reported to the sponsor as per SAE reporting requirements and timelines (see Section 9.2) if it is considered reasonably possibly related to study procedure.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. Subjects with a serious hepatic AE should have additional data collected using the CRF.

Pregnancy (during maternal or paternal exposure to investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements, any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued and/or completed the study (the subject disposition CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

9.2.1.1. Severe Hypoglycemia

Severe hypoglycemia is defined as an event accompanied by neuroglycopenic symptoms that result in cognitive impairment such that the patient requires assistance of another person to actively administer carbohydrate, glucagon, or perform other resuscitative actions. During these episodes, the patient has an altered mental status, and cannot assist in their care, is semiconscious or unconscious, or experienced coma with or without seizures, and may require parenteral therapy. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of self-monitored blood glucose (SMBG) concentration to normal is considered sufficient evidence that the event was induced by a low SMBG concentration (≤70 mg/dL).

Documented symptomatic hypoglycemia is defined as an event that is accompanied by signs/symptoms of hypoglycemia, and is accompanied by a measured SMBG concentration of ≤70 mg/dL.

9.2.1.2. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the USPI and that the investigator identifies as related to investigational product(s) or procedure. Lilly has procedures that will be followed for the identification, recording, and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.2. Adverse Device Effects

The investigator is responsible for sending to the sponsor within 24 hours any and/or associated product complaints involving a device malfunction of the pen, using the AE process and associated complaint report. Lilly will investigate all (S)AEs and associated complaints to determine the extent to which the event was caused by, or associated with, the investigational device.

Lilly will follow procedures consistent with US regulations to confirm and handle any unanticipated adverse device effects (UADEs), and will inform the Food and Drug Administration of confirmed UADEs following an investigation of the event. Within 10 working days of learning of the event, the principal investigator will then report evaluation results for any UADE to all reviewing Institutional Review Boards.

All UADEs will be summarized in the final study report.

9.2.3. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Specifically, a product complaint is an expressed (written or verbal) statement regarding a deficiency in the expected performance of the device (e.g., did not work as intended; malfunctioned; difficult to use). A product complaint may occur independently from an AE, or along with an AE. A product complaint may also occur independently of a device malfunction.

The site is responsible for collecting all product complaints and reporting these to the sponsor via the provided product complaint form template. Device malfunctions on any Lilly product (e.g., failure of the investigational device to perform as intended) will be reported to the sponsor, irrespective of whether associated with an AE.

The investigator must instruct subjects to contact the clinical site as soon as possible if he or she has a complaint or problem with the product, investigational reusable insulin injection pen, or the commercially available CGM device so that the situation can be assessed.

All investigational reusable devices associated with complaints must be returned to the sponsor for evaluation.

9.3. Treatment of Overdose

Refer to product labeling for insulin lispro 100 units/mL (USPI).

9.4. Safety

9.4.1. Laboratory Tests

For each subject, the local laboratory test for HbA1c should be conducted according to the SOA (Table IOQV.1). A pregnancy test may be performed at the investigator's discretion if there is suspicion of possible pregnancy.

9.4.2. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

10. Statistical Considerations

10.1. Sample Size Determination

Approximately 68 subjects may be entered (i.e., signed informed consent) in order that 50 subjects complete the study. Subjects who are entered but not administered treatment may be replaced to ensure that enough subjects may complete the study. Assuming a screen fail rate of 15%, the expected number of subjects to be screened is 80. Up to 15 subjects may be enrolled at each investigator site.

A sample size of 50 completers (approximately 25 subjects with T1D and 25 subjects with T2D) is considered sufficient for this exploratory study.

10.2. Populations for Analyses

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

Table IOQV.4.   **Analysis Sets**

Analysis Set	Description
Entered	All participants who signed informed consent
Evaluable	All enrolled subjects with ≥2-week use of unblinded CGM
Safety	All enrolled subjects with any CGM or pen usage

Abbreviation: CGM = continuous glucose monitoring.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee.

Efficacy analyses will be conducted on the evaluable analysis set and safety analyses on the safety analysis set defined in Table IOQV.4.

Given the exploratory nature of the study, the analyses will be primarily descriptive, using descriptive statistics (mean, standard deviation [SD], minimum, median, and maximum for continuous variables; frequency and percentage for categorical variables) or graphs (e.g., scatter plot).

Missed bolus doses and glucose time-in-range will be calculated for Weeks 3-6 for Study Period 1 (blinded CGM) and Weeks 9-12 for Study Period 2 (unblinded CGM).

Any change to 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 clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

10.3.1.1. Treatment Group Comparability

10.3.1.2. Subject Disposition
The primary reasons for discontinuation will be summarized by study period and subject allocation will be summarized by investigative site for the entered analysis set.

10.3.1.3. Subject Characteristics
Baseline characteristics will be summarized for the entered analysis set and the evaluable analysis set.

10.3.1.4. Treatment Compliance
Amount of useable data from the CGM device and pen will be summarized for the evaluable analysis set.

10.3.2. Efficacy Analyses

10.3.2.1. Primary Analyses
The average number of days per month with a missed bolus dose during the last 3 weeks of Study Period 1 will be summarized. The 3 weeks of data will be adjusted to a 1-month interval, and a 95% confidence interval will be calculated.

10.3.2.2. Secondary Analyses
The percent glucose time-in-range (>70 and ≤180 mg/dL) will be calculated and summarized for Study Period 1 and Study Period 2. The number of missed bolus doses (average number of missed bolus doses per day) as well as the percent of missed bolus doses (adjusted to a 1-month interval) will be summarized by Study Period 1 and Study Period 2. The MSBD will be summarized by Study Period 1 and Study Period 2.

10.3.3. Safety Analyses
Adverse events including discontinuations due to AEs and SAEs will be summarized.

10.3.4. Other Analyses
Patient reported outcomes rated on the Likert scale will be summarized using frequency and percentage. Domain or total scores will be summarized using: n, mean, SD, minimum, median, maximum at the times outlined in the SOA (Table IOQV.1).

In addition, bolus dose, basal insulin dose information, and exposure will be summarized.

10.3.4.1. Subgroup Analyses
The average number of missed bolus doses per month will be summarized for the following baseline subgroups:

- Glucose time-in-range (≤median vs. >median);
- HbA1c (≤9.0% vs. >9.0%);
- Duration of diabetes (≤median vs. >median);
- Prior CGM experience (yes vs. no).

10.3.5. Interim Analyses

No interim analyses are planned for this study.

11. References

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12. Appendices

Appendix 1.   Abbreviations and Definitions

Term	Definition
AE	adverse event: Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALBSS	Adult Low Blood Sugar Survey
BFI	The Big Five Inventory
CGM	continuous glucose monitoring
CIOMS	Council for International Organizations of Medical Sciences
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRF	case report form
CSR	clinical study report
enroll	The act of assigning a subject to a treatment. Subjects who are enrolled in the study are those who have been assigned to a treatment.
enter	Subjects entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
FOIA	Freedom of Information Act
GCP	good clinical practice
GLSS	General Life Stress Scale
HbA1c	glycated hemoglobin
HCS	Hypoglycemic Confidence Scale
HPSS	Health Problem Solving Scale
IB	Investigator's Brochure

Term	Definition
ICF	informed consent form
ICH	International Council for Harmonisation
Informed consent	A process by which a subject voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IOQV	F3Z-MC-IOQV
Malfunction	Any failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed.
MSBD	missing and suboptimal bolus dose
PRISM R II	Pictorial Representation of Illness and Self Measure Revised II
PRO/ePRO	patient-reported outcomes/electronic patient-reported outcomes
SAE	serious adverse event
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SD	standard deviation
SMBG	self-monitored blood glucose
SOA	Schedule of Activities
SUSARs	suspected unexpected serious adverse reactions
T1D	type 1 diabetes
T2D	type 2 diabetes
UADE	Unanticipated Adverse Device Effect: Any 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 subjects.

Term	Definition
US	United States
USPI	United States Package Insert

Appendix 2.   Study Governance Considerations

Appendix 2.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Appendix 2.1.1.   Informed Consent

The investigator is responsible for:

- ensuring that the subject or the subject's legal representative understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.

- ensuring that informed consent is given by each subject or legal representative. This includes obtaining the appropriate signatures and dates on the informed consent form (ICF) prior to the performance of any protocol procedures and prior to the administration of investigational product.

- answering any questions the subject or the subject's legal representative may have throughout the study and sharing in a timely manner any new information that may be relevant to the subject's or the subject's legal representative's willingness to continue his or her participation in the study.

- ensuring that a copy of the ICF is provided to the participant or the participant's legal representative and is kept on file.

- ensuring that the medical record includes a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Appendix 2.1.2.   Recruitment

Lilly is responsible for the central recruitment strategy for subjects. Individual investigators may have additional local requirements or processes.

Appendix 2.1.3.   Ethical Review

The investigator or an appropriate local representative must give assurance that the ethical review board (ERB) was properly constituted and convened as required by International Council for Harmonisation (ICH) guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on Good Clinical Practice (GCP).

The study site's ERB(s) should be provided with the following:

- the protocol and related amendments and addenda, current Investigator's Brochure, United States Product Information, training checklist, and updates during the course of the study

- the ICF

- other relevant documents (for example, curricula vitae, advertisements)

Appendix 2.1.4.   Regulatory Considerations

This study will be conducted in accordance with the protocol and with the:

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines

- applicable ICH GCP Guidelines

- applicable laws and regulations

Some of the obligations of the sponsor will be assigned to a third party.

Appendix 2.1.5.   Investigator Information

Physicians with a specialty in endocrinology, diabetology, and/or primary care will participate as investigators in this clinical trial.

Appendix 2.1.6.   Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

Appendix 2.1.7.   Final Report Signature

The investigator will sign the final clinical study report (CSR) for this study, indicating agreement with the analyses, results, and conclusions of the report.

The sponsor's responsible medical officer and statistician will approve the final CSR for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Appendix 2.2.   Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate

- sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the case report forms (CRFs), and study procedures.

- make periodic visits to the study site

- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax

- review and evaluate CRF data and use standard computer edits to detect errors in data collection

- conduct a quality review of the database

In addition, Lilly or its representatives will periodically check a sample of the subject data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

Appendix 2.2.1.   Data Capture System

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

Paper and electronic patient-reported outcomes (ePRO) measures or other data reported directly by the subject are entered into an ePRO instrument at the time that the information is obtained. In these instances where there is no prior written or electronic source data at the site, the ePRO instrument record will serve as the source.

If ePRO records are stored at a third-party site, investigator sites will have continuous access to the source documents during the study and will receive an archival copy at the end of the study for retention.

Any data for which the ePRO instrument record will serve to collect source data will be identified and documented by each site in that site's study file.

Case report form data will be encoded and stored in a clinical trial database.

Case report form data collected by a third party will be encoded by the third party and stored electronically in the third-party's database system. Validated data will subsequently be transferred to the sponsor's data warehouse using standard Lilly file transfer processes.

Any data for which paper documentation provided by the study participant will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the study participant may include, for example, a paper diary to

collect patient-reported outcomes measures (for example, a rating scale), a daily dosing schedule, or an event diary.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

Appendix 2.3. Study and Site Closure

Appendix 2.3.1. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly or its designee, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 2.3.2. Discontinuation of the Study

The study will be discontinued if Lilly or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 3.   Classification of Contraceptive Methods

Highly Effective Methods of Contraception:

- Combined oral contraceptive pill and mini-pill
- NuvaRing
- Implantable contraceptives
- Injectable contraceptives (such as Depo-Provera®)
- Intrauterine device (such as Mirena® and ParaGard®)
- Contraceptive patch – ONLY women <198 pounds or 90 kg
- Total Abstinence
- Vasectomy – for men in clinical trials

Effective Methods of Contraception (must use combination of 2 methods):

- Male condom with spermicide
- Female condom with spermicide
- Diaphragm with spermicide
- Cervical sponge
- Cervical cap with spermicide

Ineffective Forms of Contraception – not acceptable as a method for clinical trials

- Spermicide alone (please note spermicide alone is not considered a barrier method)
- Immunocontraceptives
- Periodic abstinence
- Fertility awareness (calendar method, temperature method, combination of above 2, cervical mucus, symptothermal)
- Withdrawal
- Post coital douche
- Lactational amenorrhea

Appendix 4. CCI
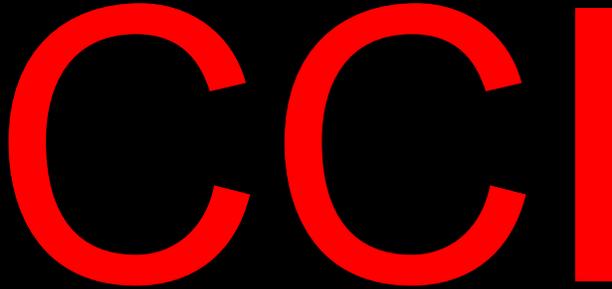
CCI

Appendix 5.   Summary of Protocol Amendments

Protocol Amendment 1, Dated 17 Nov 2017

Section	Summary of Changes
2 Schedule of Activities	Negative pregnancy test added as a required activity to be conducted during screening (Visit 1)
6.1 Inclusion Criteria [5b]	Definitions of women of child-bearing potential added to the inclusion criteria
Appendix 3	Classification of contraceptive methods added
Appendix 4 – CCI	Information on CCI and the use of mobile nurses