Protocol Addendum F3Z-MC-IORW(f)

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

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Protocol F3Z-MC-IORW(f)

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

Confidential Information

Tempo Pen and Tempo Smart Button LY8888AX
in support of Humalog (insulin lispro) LY275585

Sponsor: Eli Lilly Cork Limited, a company incorporated under the laws of the Republic of Ireland with company registration number 615384, having a registered office at Island House, Eastgate Road, Eastgate Business Park, Little Island, Co. Cork Ireland, serves as the "Legal Representative" for all clinical investigations sponsored by Eli Lilly and Company conducted within the EU pursuant to the Medical Device Regulation (EU 2017/745) and applicable country legislation.

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Protocol Amendment Summary of Changes

This amendment is considered to be non-substantial.

Changes made in this protocol amendment reflect the change from ‘up to 10 sites’ to the specific number of sites in France.

Section Number and Name	Description of Change
1. Protocol Summary	• Text for number of sites amended to state 9 sites in France.
4.1 Overall Design	• Text for Number of Sites amended to state that the study will include 9 sites in France.

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1. Protocol Summary

1.1. Synopsis

Study Title:	Assessment of Participant Adherence and Glucose Control While Using a Connected Insulin Management Platform
Study Funding:	Eli Lilly and Company
Study Description:	18-week, 1 country, multicentre, open-label, controlled, single-arm, pragmatic outpatient study to assess participant adherence and glucose control while using a connected insulin management platform
Participant Population:	≥18 years old diagnosed with type 1 diabetes (T1D) or type 2 diabetes (T2D) on basal bolus therapy with a glycated haemoglobin (HbA1c) ≥8%
Sample Size	Approximately 50 total study participants
Number of Sites	9 sites in France
Study Duration	Approximately 16 months
Participant Duration	Approximately 18 weeks
Study Platform Description	Conformité Européenne (CE) marked devices: • Lilly Tempo Smart Button™, attached to the Tempo Pen™, will be used to detect and transmit CCI [redacted] data CCI [redacted] to the Glooko Research Mobile Application (RMA). • Dexcom® G6 continuous glucose monitoring (CGM) will be used to monitor interstitial glucose throughout the study. • The study is divided in 2 periods; (1) Masked CCI [redacted] Data (run in): first 6 weeks and (2) Unmasked CCI [redacted] Data (intervention): Week 7 to 18. CE-marked medical device software (MDSW): • The Glooko RMA for people with diabetes (PwD), will be used to receive CCI [redacted] data from the Tempo Smart Button and CGM to track insulin dosing history and interstitial glucose values and share them with healthcare professionals (HCPs). • Glooko platform for HCPs, will be used to share and consolidate participants' data from Glooko RMA with HCPs. Approved Medicinal Product: • Lilly Tempo Pen will be used to subcutaneously administer Humalog® insulin to treat adults with T1D or T2D on basal bolus therapy.
Objectives and Endpoints	Primary Objective: To compare the number of missed bolus doses (MBDs) during the Study Period 2 (Weeks 15 to 18), compared to the Study Period 1 (Weeks 5 and 6) in participants using the Primary Endpoint: Difference in the average number of MBDs per week in the masked versus unmasked portions of the study.

	• Tempo Pen • Tempo Smart Button • Glooko RMA, and • Dexcom G6 CGM.	*Missed bolus dose 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 was 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 Objectives: 1) To evaluate difference in participant CGM time-in-range (TIR) (≥70 to 180 mg/dL) in the Study Period 1 versus Study Period 2. 2) To evaluate difference in participant CGM time above range (TAR) (>180 mg/dL and >250 mg/dL) in the Study Period 1 versus Study Period 2. 3) To evaluate difference in participant CGM time below range (TBR) (54 mg/dL ≤ TBR < 70 mg/dL and < 54 mg/dL) in the Study Period 1 versus Study Period 2. 4) To evaluate Coefficient of Variation and mean sensor glucose from CGM values 5) To examine occurrence and change of mistimed boluses between Study Period 1 versus Study Period 2. 6) To evaluate the change in total insulin doses (basal, mealtime per meal type, correction bolus) Study Period 1 versus Study Period 2 7) To evaluate occurrence, change, and Study Period 1 versus Study Period 2 change in correction boluses 8) To examine the association between MBD and TIR, TAR, TBR, HbA1c 9) To examine the association between mistimed bolus and TIR, TAR, TBR, HbA1c 10) To assess device preference, satisfaction, convenience, and ease of use	Secondary Endpoints: 1) CGM TIR (≥70 to 180 mg/dL) in the masked versus unmasked portions of the study. 2) CGM TAR (>180 mg/dL and >250 mg/dL) in the masked versus unmasked portions of the study. 3) CGM TBR (54 mg/dL ≤ TBR < 70 mg/dL and < 54 mg/dL) in the masked versus unmasked portions of the study. 4) Coefficient of variation and mean sensor glucose from CGM data collected from each participant 5) Occurrence and change of mistimed boluses 6) 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. 7) Occurrence, change, and masked versus unmasked change in correction boluses 8) CGM curves integrated with data received from the Tempo Pen 9) CGM curves integrated with data received from the Tempo Pen 10) Participant and HCP questionnaires

1.2. Schema

Figure 1.1 gives an outline of the study schema.

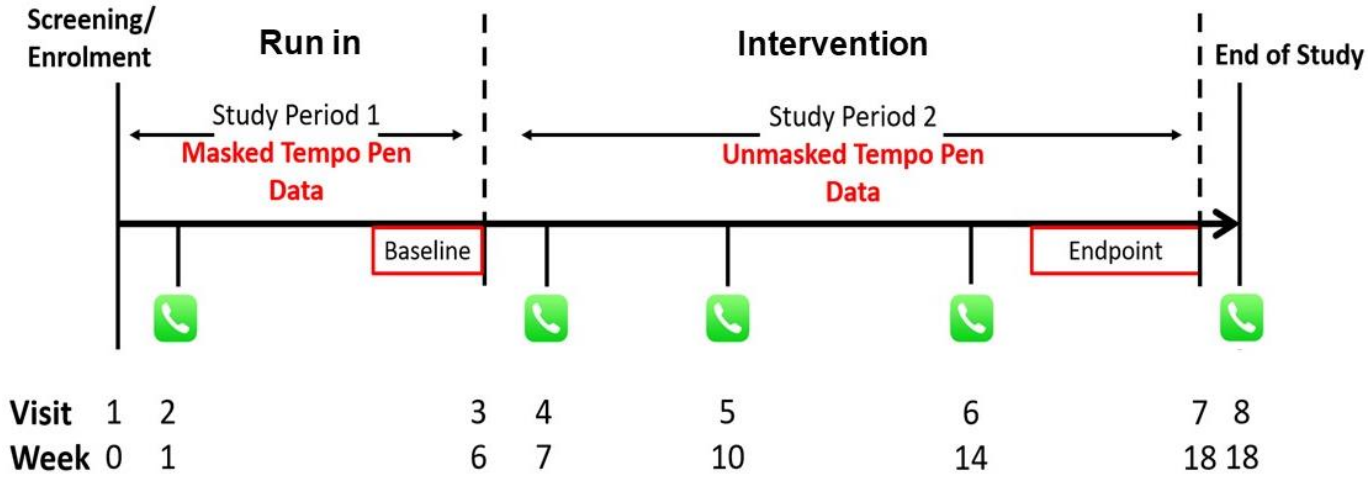


Figure 1.1. Schema for Study IORW.

1.3. Schedule of Activities

Table 1.1 summarises the Schedule of Activities (SoA) for the study.

Table 1.1. Schedule of Activities for Study F3Z-MC-IORW

	Study Period 1 (Masked)			Study Period 2 (Unmasked)				Follow-up	UNS	ET
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8 or ET(Exit)**		
Visit Type	On-site	Remote	On-site	Remote	Remote	Remote	On-site	Remote		
Time from previous visit (weeks or days)	N/A	1 W	5 W	1 W	3 W	4 W	4 W	3D	N/A	N/A
Visit window (days)	N/A	+/-3	+7	+/-3	+/-3	+/-3	+7	+/-1	N/A	N/A
Study Logistics										
Informed Consent signed	X									
Eligibility Criteria Reviewed	X									
Enrolment	X									
Install and set-up Glooko RMA	X									
Pair the Tempo Smart Button	X									
Study CGM device user training provided	X									
Study phone user training provided	X									
Complete Participant Training	X									
Participant brings mobile device with RMA and Tempo Pen with Tempo Smart Button			X				X			X
Confirm Tempo Smart Button transfer onto Glooko RMA			X[1]		X[1]	X[1]	X[1]		X[1]	X[1]
Review the functioning, understanding, and use of the study platform components	X	X	X	X	X[2]	X[2]			X[2]	

	Study Period 1 (Masked)			Study Period 2 (Unmasked)				Follow-up	UNS	ET
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8 or ET(Exit)**		
Visit Type	On-site	Remote	On-site	Remote	Remote	Remote	On-site	Remote		
Time from previous visit (weeks or days)	N/A	1 W	5 W	1 W	3 W	4 W	4 W	3D	N/A	N/A
Visit window (days)	N/A	+/-3	+7	+/-3	+/-3	+/-3	+7	+/-1	N/A	N/A
Unmask Tempo Pen data in Glooko RMA			X							
Clinical Assessment and Diabetes Management										
Medical History (including pre-existing conditions)	X									
Demographic information	X									
Height and Weight	X		X[3]				X[3]			X[3]
Physical Examination	X									
Urine PoC Pregnancy Test (WOCBP only)	X									
HbA1c PoC Test	X						X			X
Vital Signs	X									
Hypoglycaemia management and training	X		X[4]		X[4]	X[4]			X[4]	QR
Review concomitant medications	X	X	X	X	X	X	X	X	X	X
Review Adverse Events	X	X	X	X	X	X	X	X	X	X
Review Device Deficiencies (DD)	X	X	X	X	X	X	X	X	X	X
Review of glucose values and insulin regimen with participant (adjust if appropriate)	X		X[5]		X[5]	X[5]	X[5]			X[5]
Document any educational activities			X[6]		X[6]	X[6]	X[6]			X[6]
Study Material Management										
Dispense Tempo Smart Button	X								X[4]	
Dispense Humalog Tempo Pens	X		X						X[4]	

	Study Period 1 (Masked)			Study Period 2 (Unmasked)				Follow-up	UNS	ET
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8 or ET(Exit)**		
Visit Type	On-site	Remote	On-site	Remote	Remote	Remote	On-site	Remote		
Time from previous visit (weeks or days)	N/A	1 W	5 W	1 W	3 W	4 W	4 W	3D	N/A	N/A
Visit window (days)	N/A	+/-3	+7	+/-3	+/-3	+/-3	+7	+/-1	N/A	N/A
Check Dexcom data transfer	X	X	X	X	X	X	X		X	
Dispense Study CGM device and receiver	X		X						X	
Review usage of Humalog Tempo Pen & Tempo Smart Button	X		X	X	X	X	X		X	
Supply Collection (as per Sponsor's instructions)							X			X
Study Questionnaires										
IORW Participant Visit 1 Questionnaire	X									
IORW Participant Visit 3 Questionnaire			X							X[7]
IORW Participant Visit 7 Questionnaire							X			X
HFS-SF Questionnaire	X		X				X			X
IORW Initial HCP Questionnaire	X[8]									
IORW End-of-study HCP Questionnaire								X[9]	N/A	N/A

Abbreviations: CGM = continuous glucose monitoring; D = day; ET = early termination; HbA1c = glycated haemoglobin; HCP = healthcare professional; HFS-SF = Hypoglycaemia Fear Survey – Short Form (Adult Low Blood Sugar Survey); N/A = not applicable; RMA = research mobile application; DD = device deficiency; PoC = point-of-care; UNS = unscheduled visit; V = visit; W = week; WOCBP = women of childbearing potential.

1 Using Glooko HCP platform.

2 If deemed necessary based on a previous visit.

3 Weight only.

4 If required.

5 Using the Glooko HCP platform.

6 Recommendations that resulted from the review of the Glooko report with the participant.

7 If the Early Termination visit takes place before Visit 3.

[8] Initial HCP Questionnaire should be completed **prior** to site's First Participant Visit (FPV).
[9] End-of-study HCP Questionnaire should be completed **after** site's Last Participant Visit (LPV).

2. Introduction

2.1. Study Rationale

2.1.1. Insulin Management for People with Diabetes

PwD face many challenges throughout their diabetes journey to reach and maintain their treatment goals. They are required to strictly manage numerous facets of their lives, such as:

- meal planning
- lifestyle considerations, and
- medical management of their condition, including:
    - appropriately adjusted insulin dosing
    - multiple medications with different dosing regimens (mainly for those with type 2 diabetes [T2D])
    - frequent glucose levels monitoring, and
    - record keeping for insulin injections timing and dosage on paper logbooks or apps.

2.1.2. Challenges with Insulin Management

People with diabetes on basal bolus insulin therapy regimen require multiple daily injections:

- mealtime (bolus) insulin once before every meal, and
- a long-acting insulin (basal insulin) once or twice daily.

Adherence to insulin therapy is important for optimal glycaemic control. The most immediate consequence of missing insulin doses at mealtime is a lack of control on post-meal glucose excursions which has deleterious effect on time-in-range as measured by CGM, but also on intermediate measures such as glycated haemoglobin (HbA1c) and long term micro- and macro-vascular complications (Andrade et al. 2017; Munshi et al. 2013; Nathan et al. 2005; Randløv and Pulsen 2008; Spaans et al. 2018).

Multiple daily insulin injections can be burdensome for PwD and, therefore, adherence challenges including missing dose opportunities to insulin therapy is frequent, both in type 1 diabetes [T1D] and T2D (Peyrot et al. 2012a) for reasons such as:

- lifestyle burden,
- difficulty with injection or the insulin regimen, and
- certain psychosocial and behavioural factors (Peyrot et al. 2012b).

HCPs and diabetes educators rely on PwD to keep paper logs or diaries of these activities to gain insights and discern patterns to make insulin therapy adjustments or provide education and training. For PwD, keeping treatment logs can be burdensome and can result in inaccurate and incomplete information for the PwD and their HCP (Kompala and Neinstein 2021).

2.1.3. Use of Connected Devices for Insulin Management

Smart insulin pens can provide the missing data to allow HCPs and PwD to inform optimised insulin treatment decisions (Adolfsson et al. 2020; Heinemann et al. 2021; Klonoff and Kerr 2018; Kompala and Neinstein 2021; Munshi et al. 2019, Sy et al. 2022). Recent American Association of Clinical Endocrinology (AACE) guidelines recommend that the use of connected pens may help patients with diabetes and clinicians:

- optimise insulin regimens, and
- avoid stacking of rapid acting insulin, which may lead to hypoglycaemia (Grunberger et al. 2021).

Studies with connected insulin pens have allowed HCPs to identify more precisely the frequency of MBDs in groups of people with T1D and T2D on CGM (Edwards et al. 2021; Adolfsson et al. 2020; Munschi et al. 2019, Gomez-Peralta et al. 2023).

Adolfsson et al. (2020) evaluated the use of a reusable insulin connected pen in the setting of a prospective multicentre observational study in Sweden, in 94 people with T1D using CGM. During the "baseline" observation period with blinded CGM, at least 25% of meals had a missed dose on average, assuming 3 meals per day. This amounted to 5 meals with a missed dose per week on average. Over an average period of 7 months, the authors could show an improvement of almost 2 hours in TIR (70-180 mg/dL), mainly due to a reduction of time above range (TAR) (>180 mg/dL). This happened thanks to an improvement of adherence to insulin therapy with 43% fewer MBDs (N = 14 patients).

Despite the low sample size, this suggests that evaluating past dosing data together with HCPs may have helped participants to remember and administer their mealtime doses, or to improve the timing of the dose, relative to the meal. The data is consistent with the hypothesis that connected pens may support people with the management of their insulin treatment regimens and help reduce missed and mistimed bolus doses.

2.1.4. Purpose of Study

Eli Lilly and Company (Lilly) has introduced a reusable CCI data transmission module (Tempo Smart Button) which can be attached to a compatible disposable single-use prefilled insulin pen (Tempo Pen).

The Tempo Pen/Smart Button facilitates an automated collection CCI [redacted] that can be put in relation with glycaemic values measured either in the capillary blood with fingersticks (self-monitored blood glucose [SMBG]) or with a CGM through a Glooko RMA.

In this study, Lilly intends to provide further and more reliable clinical evidence to confirm what was observed in the Adolfsson study, focusing on showing a reduction of MBDs in a controlled single-arm study enrolling people with uncontrolled diabetes (HbA1c ≥8%), both T1D and T2D on basal bolus therapy. Patients with T2D were not included in the Adolfsson study and it is believed that T2D patients on basal bolus therapy could also benefit from a connected insulin

management platform (Grunberger et al. 2021). Study F3Z-MC-IORW (IORW) seeks to understand the relationship between the use of a connected insulin platform and people's own daily diabetes management such as:

- adherence to insulin regimen (MBD)
- timing of injection (mistimed bolus)
- daily insulin dose adjustment, and
- glycaemic outcomes.

Study IORW will assess the number of MBDs during the Study Period 2 (Weeks 15 to 18), compared to the Study Period 1 (Weeks 5 and 6) in participants using the:

- Humalog Tempo Pen
- Tempo Smart Button
- Glooko RMA, and
- Dexcom G6 CGM.

Study IORW will be an open-label, single arm, pragmatic study, conducted with participants in an outpatient setting with study interventions representative of standard clinical practices, to minimise bias associated with participation in a clinical trial. By utilising insulin dosing and interstitial glucose data, this study should allow Lilly to assess the impact of connected platforms on diabetes management.

2.2. Components of Study Platform

The study platform to be used (Figure 2.1) is comprised of the following components:

Conformité Européenne- (CE-) marked devices:

- Tempo Smart Button (Lilly), and
- Dexcom G6 (Dexcom) CGM.

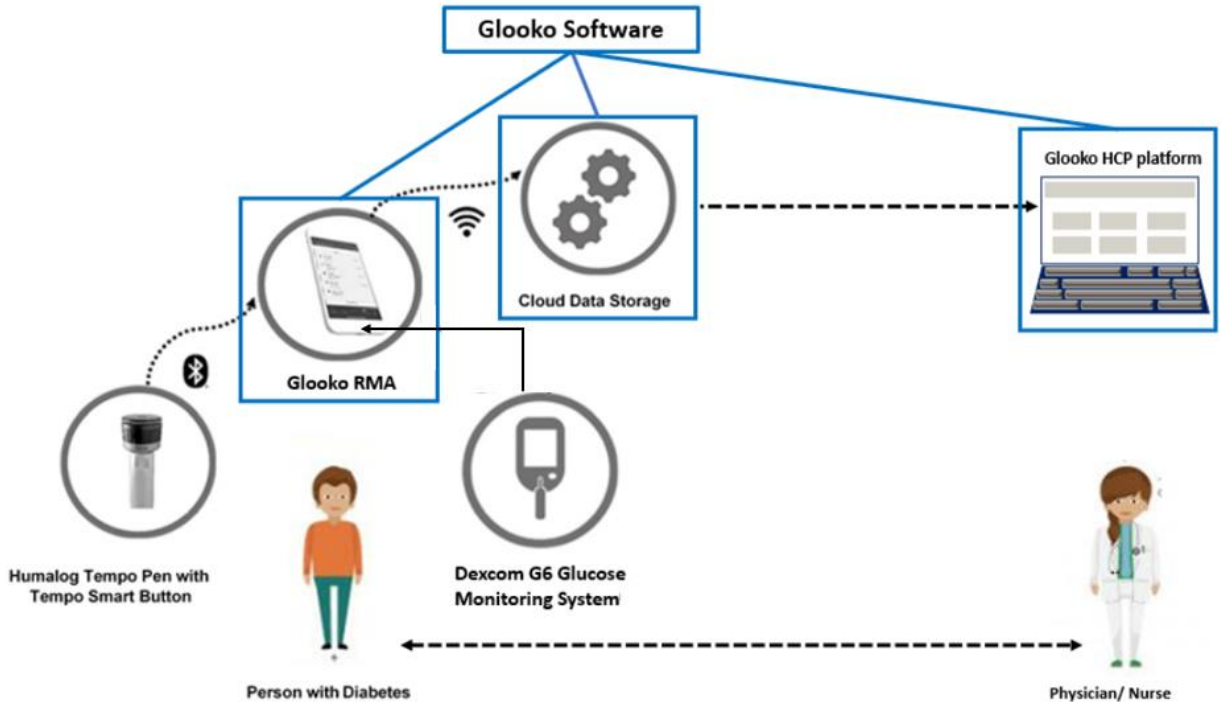
Approved Medicinal Product:

- Humalog® Tempo Pen (Lilly).

CE-marked MDSW:

- Glooko MDSW (Glooko Inc.) installed on the study-provided Android smartphone, consisting of:
    - Glooko RMA for PwD
    - Glooko HCP platform

Data from the Glooko MDSW will be stored in cloud data storage through which the data is shared between PwD and HCPs.



Abbreviations: HCP = healthcare professional; RMA = research mobile application.

Figure 2.1. Components of study platform.

CCI data from the Tempo Pen/Smart Button are wirelessly transmitted to the Glooko RMA via Bluetooth. Interstitial glucose values from the Dexcom G6 CGM are transmitted periodically via USB cable. The participant may also track data such as basal insulin delivery, exercise, and carbohydrate or meal intake on the RMA.

Data from the study platform components gathered in the Glooko RMA provides the participant with information to:

- assess omitted or suboptimal dose data
- get access retrospectively to his/her own data in case he/she needs to, and
- provide the participant with an opportunity for productive and objective discussion with his/her HCPs to better adjust insulin treatment and optimise the way he/she manages his/her diabetes.

User-tracked data will be available to HCP through the Glooko HCP platform which can:

- provide an objective history of user's own diabetes management, and
- generate meaningful conversations between the user and HCP to improve insulin treatment (e.g., reduce the number of missed boluses, discuss impact of injection timing,

and also help users learn how to adjust insulin doses) and ultimately improve glycaemic outcomes.

2.3. Description of Devices

The devices used in the study are described in the following sections.

2.3.1. *Commercial Devices and Products*

2.3.1.1. Tempo Smart Button

The Tempo Smart Button (manufactured by Lilly, Indianapolis, IN USA) is a reusable data transmitter (or data transfer module) that:

- detects and stores information from a Tempo Pen, and then
- transfers insulin dose-related data to a compatible mobile application via Bluetooth® wireless technology.

The dose-related data corresponds to the brand of insulin, dose amount, date, and time. Figure 2.2 provides an illustration of the Tempo Smart Button.

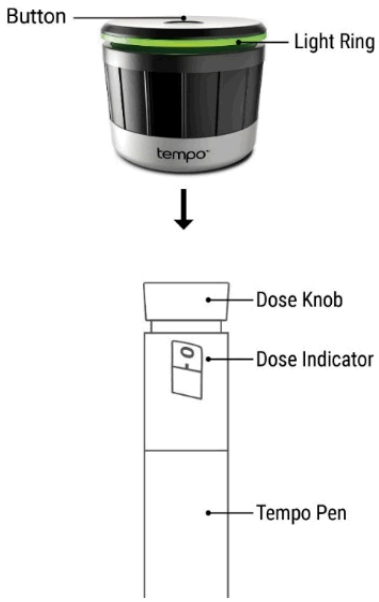


Figure 2.2. Tempo Smart Button.

The Tempo Smart Button is designed to be attached and detached from a Tempo Pen and is only functional when attached to a Tempo Pen.

When paired with an RMA, the Tempo Smart Button transmits stored data CCI [redacted] the RMA user interface. The Tempo Smart Button is designed so that no outside information or data can be received by the Smart Button. The communication is only in one direction: from

the Tempo Smart Button to the RMA. It is not possible to use the RMA to modify the CCI [redacted] data stored on the Tempo Smart Button.

Once the Tempo Smart Button module is paired to the RMA on the study-provided mobile device, the module will automatically transfer data to the RMA after a dose is delivered, as long as:

- the user has placed the Tempo Smart Button in the proximity of the paired mobile device
- Bluetooth is enabled on the participant's mobile device, and
- the RMA is launched and open.

If the Tempo Smart Button is not in proximity of the mobile device before Bluetooth Low Energy (BLE) shuts down, then the data will be transferred the next time that the Tempo Smart Button is activated, and the RMA is open (that is, data are not lost). The dose records, up to a total of 5840 (Tempo Smart Button IFU) remain in the Smart Button data storage for the life of the module; dose records are not deleted after transmission to the RMA.

The Tempo Smart Button to be used in this study will be the CE-marked presentation (Class I EU MDR).

2.3.1.2. Humalog Tempo Pen

Humalog (Lilly) is a rapid acting human insulin analogue used in the treatment of adults and children with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis. Humalog is also indicated for the initial stabilization of diabetes mellitus.

The Humalog Tempo Pen (manufactured by Lilly, Indianapolis, IN USA) is used for the subcutaneous administration of insulin.

The Humalog Tempo Pen (Figure 2.3) is a disposable single-patient-use prefilled pen (medicinal product) that comprises:

- Humalog insulin (insulin lispro);
- a dose knob that allows for attachment of the Tempo Smart Button module; and

- an embedded magnet that allows the Tempo Smart Button module to detect the Tempo Pen. Once the Tempo Smart Button detects the Tempo Pen, the Tempo Smart Button will be activated.

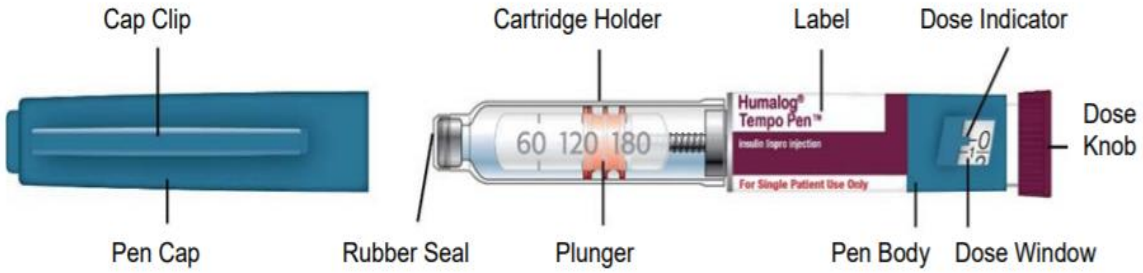


Figure 2.3. Humalog Tempo Pen.

The Humalog Tempo Pen to be used in this study is the EC-approved presentation and will be provided as a 100-units/mL solution in a 3-mL Humalog Tempo Pen.

2.3.1.3. Dexcom G6 Continuous Glucose Monitor

The Dexcom G6 Continuous Glucose Monitor (also referred to as CGM; manufactured by Dexcom, Inc, San Diego, CA, USA) is a glucose monitoring system indicated for persons aged 2 years and older, including pregnant women. The Dexcom G6 system is intended for use by patients at home and in healthcare facilities.

The Dexcom G6 CGM is designed to replace fingerstick blood glucose (BG) testing for treatment decisions. The system also aids in the detection of episodes of hyperglycaemia and hypoglycaemia, facilitating both acute and long term therapy adjustments.

The Dexcom G6 sensor inserted under the skin checks glucose levels in interstitial fluid and the transmitter sends readings to the receiver, where user can read the glucose values in real time.

The CGM G6 Glucose Monitoring System to be used in this study will be the commercially available, CE-marked presentation (Class IIb EU MDD [Dexcom Letter of Conformity Form]).

The Dexcom G6 CGM system (Figure 2.4) consists of 3 main components:

- Applicator with built-in sensor - a small sensor which is worn on the back of the user's upper arm or belly. The sensor applicator is used to insert the sensor under the skin. The sensor then gets the glucose information. The sensor can be worn for up to 10 days, after which it automatically stops working and must be replaced.
- Transmitter – attaches to the sensor holder and sends glucose information from sensor to display device (receiver or smart device). If connection is lost between the transmitter and display device, up to 3 hours of data will be transmitted from the transmitter to the display device upon re-connection. Once snapped into place, the transmitter is water

resistant. The transmitter is reusable, lasts 3 months, and can be re-used with multiple sensors.

- Receiver – a rechargeable, display device which is used to receive the data from the Dexcom G6 transmitter. The data transmitted from the transmitter is presented to the user as a graph and glucose level trend indications are also available.
- Smart Device – a rechargeable, study-provided, Android smartphone which is used to receive the data from CCI Glooko RMA (via USB cable).

Figure 2.4. Components of Dexcom G6 CGM System.

2.3.1.4. Glooko Medical Device Software

Glooko RMA and Glooko HCP platform will be used in the study to track participant's insulin dosing data CCI and interstitial glucose values from the Dexcom G6 CGM. Data (including basal insulin delivery, carbohydrate or meal intake, exercise) will be shared with HCP through the Glooko HCP platform to generate meaningful conversations between the participant and HCP to improve insulin treatment (e.g., reduce the number of missed boluses, discuss impact of injection timing, and also help users learn how to adjust insulin doses) and ultimately improve glycaemic outcomes.

2.3.1.4.1. Glooko research mobile application

Glooko Research Mobile Application (Glooko Inc.) is a CE-marked (Class I EU MDD) software for PwD to aid in management of T1D (adults and children), T2D, and gestational diabetes.

The Glooko RMA is designed to receive and display user data as part of self-management of diabetes. Data in Glooko RMA can be manually input by the user (e.g., meals, physical exercise,

basal insulin delivery) transferred from connected devices via Bluetooth CCI [redacted], or uploaded via USB cable from non-connected devices (e.g. CGM readings). The Glooko RMA is a modified version of the commercial app that includes the data masking function.

The Glooko RMA also contains the following functionalities to support the study design:

User Information

The Glooko RMA/Glooko platform allows the assignment of participant ID numbers to identify study participants and study data while protecting privacy during the trial.

Masking Tempo Smart Button and Pen Details

During Study IORW Period 1 (6 weeks, Visits 1, 2, and 3), participants will be masked to the data CCI [redacted]. Masking during Study Period 1 is necessary to obtain baseline data for bolus self-administration and dosing adjustments performed by the participant.

The Glooko RMA will be installed on the study-provided mobile phone running Android (Version 6.0 or higher) operating system with passcode protection. The mobile device will be configured to limit use to study-specific activities.

Participants will be provided with a study-specific, password-protected user account for the Glooko RMA. Healthcare professionals use their own Glooko HCP secured platform/portal to access the users' data and provide treatment advice and prescriptions during a remote or in-person medical appointment.

The data will be converted and presented in Glooko RMA in a graphical summary to the study participants. Additionally, participant's diabetes management data will be made available to HCPs through Glooko HCP platform via cloud connection.

2.3.1.4.2. Glooko HCP Platform

The Glooko Research platform allows site administrators to view all participant data in a near real time basis as data is being uploaded remotely by the users from the Glooko RMA.

2.3.1.4.3. Glooko cloud data storage

Glooko Data storage is Health Insurance Portability and Accountability Act- (HIPAA-) and General Data Protection Regulation- (GDPR-) compliant. Data storage for the European Union (EU) is in Germany for French participants. Data is transferred from the Glooko RMA to the Glooko cloud via secure cloud transfer that is encrypted in transit and at rest.

2.4. Benefit/Risk Assessment

This study will be conducted with products within their respective intended use and indication for use in a way representative of their routine, everyday use, and routine

interventions/examinations for PwD. It is anticipated that the probability and severity of any potential harm or discomfort to the study participants will be no greater than those ordinarily encountered in daily life or during the performance of routine examinations and interventions for PwD.

2.4.1. *Clinical Benefit*

With the aid of methods and devices used in this study, some participants may improve glycaemic control as a result of:

- reduction of MBDs
- ability to reliably and objectively track and view data on insulin dosing CCI [redacted] and CGM leading to more accurate insulin dose adjustments and disease understanding during unmasked Study Period
- availability of other tracking features in Glooko RMA, and
- more interactions with HCP via regular remote visits during the trial period engaging in productive conversations based on reliable, objective data to better manage the disease.

The results of this study will:

- offer valuable insights into the potential advantages of the connected devices in insulin treatment and diabetes management, and
- provide further and more reliable clinical evidence to confirm what was observed in Adolfsson et al. (2020) study, focusing on showing a reduction of MBDs, and potential improvement in TIR, for patients with T1D as well as T2D on basal bolus therapy.

In addition, the objective collection of bolus dosing data CCI [redacted] will help to better understand actual dosing behaviour in relation to the assessment of interstitial glucose values measured by the commercially available CGM device used by the person. The completion of participant behaviour and satisfaction questionnaires will help to better understand user behaviour for daily diabetes management (timing of insulin injection, missing bolus, etc.) and its relationship with bolus dosing.

As a result, it is anticipated that the productive conversations between the study participant and HCP, based on the data generated by the connected study platform, may result in a reduction of MBDs and improvement in participant's own diabetes management.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of using a connected insulin management platform may be found in the Investigator's Brochure.

2.4.2. *Potential Risks*

Potential Risks Associated with Diabetes Disease State and Insulin Treatment

- Hyperglycaemia: the symptoms of hyperglycaemia include: nausea, vomiting, abdominal pain, difficulty breathing, a fruity smell of the breath, dry or flushed skin, and confusion,

difficulty paying attention, and in severe cases, diabetic ketoacidosis (DKA). Diabetic ketoacidosis can include: excessive thirst, frequent urination, nausea and vomiting, weakness or fatigue, shortness of breath, fruity-scented breath, high blood sugar level, high ketone levels in urine.
- Hypoglycaemia: the symptoms of hypoglycaemia can include low energy, hunger, confusion, pounding heart, sweating, shakiness, headache, seizures, loss of consciousness, and coma.

Potential Risks Associated with the Study Platform

- Hyperglycaemia and/or hypoglycaemia, severe or otherwise, due to user insulin dosing behaviour negatively impacted by the study platform components resulting in overdose, underdose, or delay in therapy may be caused by:
    - incorrect or missing data stored or sent to Glooko RMA
    - repeated injection due to Tempo Smart Button or CGM malfunction
    - user misunderstanding or confusion caused by platform components, or
    - user inability to effectively use the platform or a component thereof.

Potential Risks Associated with Tempo Smart Button

- Incorrect insulin dose due to the:
    - user not pushing the Smart Button straight down during injection, or
    - Smart Button not flashing 3 times resulting in the user repeating the injection.
- Personal harm or device damage by tampering with the Tempo Smart Button, device battery or exposing the Tempo Smart Button to:
    - strong electromagnetic field (e.g., magnetic resonance imaging [MRI])
    - moisture, or
    - excessive light.
- Choking can occur with Tempo Smart Button. If inhaled or ingested, the Smart Button may cause internal injury which could require medical assistance.

For additional information please refer to the Tempo Smart Button Instructions for Use (IFU).

Potential Risks Associated with Humalog Tempo Pen

- Severe, life-threatening generalised allergy, including anaphylaxis, to Humalog insulin.
- Pain, bruising, scarring, and infection resulting from insulin injections.
- Lipodystrophy and cutaneous amyloidosis can occur due to incorrect injection technique.
- Minor skin irritation, sensitisation, or localised inflammatory response can occur if skin contacts bioincompatible materials.
- Hypokalaemia.
- People with renal impairment may be at increased risk of hypoglycaemia and may require more frequent Humalog dose adjustment and more frequent glucose monitoring.

- People with hepatic impairment may be at increased risk of hypoglycaemia and may require more frequent Humalog dose adjustment and more frequent glucose monitoring.
- The Tempo Pen contains a magnet; fitted medical devices, such as a heart pacemaker, may not work correctly if the Tempo Pen is held too close; the magnetic field extends to approximately 1.5 cm.

The occurrence and severity of these events are not expected to be different from routine use of insulin injection systems.

More detailed information about the known and expected benefits and risks and reasonably expected AEs may be found in Humalog Package Insert and Humalog Summary of Product Characteristics.

Potential Risks Associated with Dexcom G6 CGM Use

- Redness, swelling, inflammation or pain at the sensor insertion site
- Electric shock if the CGM transmitter is damaged
- Choking can occur with transmitter
- Inaccurate readings due to incorrect use of the system, damaged system components, dialysis treatment, critical illness, treatment with hydroxyurea, and
- Personal harm or device damage exposing the sensor to strong magnetic field or heat (e.g., MRI, computed tomography [CT] scan, diathermy).

The occurrence and severity of these events are not expected to be different from routine use of CGM.

More detailed information about the known and expected benefits and risks and reasonably expected AEs may be found in Dexcom G6 IFU.

Possible Risks Associated with Glooko RMA Use

- Participants must be within 6 metres of the Glooko RMA in order for the Tempo Smart Button data to transfer to their Glooko Research account.
- Participants will be able to view CCI [redacted] data (number of units of Humalog delivered and date and time stamp details) via the Glooko RMA ONLY during study period 2.

The Dexcom Clarity or Dexcom G6 applications cannot be used. Participants must periodically upload their CGM data from the Dexcom receiver to the Glooko RMA. Data will not be visible in the Glooko RMA or the HCP Portal until participants have uploaded the data. Data must be uploaded at least every 30 days or it will no longer be available in the receiver. More detailed information about the known and expected benefits and risks may be found in Glooko App IFU.

Possible Risks Associated with Participation in the Clinical Study

- Loss of confidentiality, or
- Disclosure of personal health information (PHI).

2.4.3. *Methods to Minimise Risks*

The device design and controls, nonclinical testing, user instructions, training material and clinical study design (including selection of participants in accordance with eligibility criteria, safety, and study monitoring activities) are intended to minimise the risks associated with participation in this study.

Specific training and mitigations related to hypoglycaemia can be found in Section 2.4.3.1.

The Glooko MDSW complies with the GDPR 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons regarding the processing of personal data and on the free movement of such data.

The user is informed about how his/her personal data will be collected and is asked to agree to terms of use when signing up for the use of Glooko RMA.

The risks have been minimised and are reasonable in relation to the potential users' benefits and importance of the knowledge to be gained about the use of the connected study platform for diabetes management. The study platform risks have been reduced to a level that is considered acceptable to meet the trial objectives and maintains a positive risk-benefit profile for participants.

2.4.3.1. Hypoglycaemia

Site personnel will review hypoglycaemia management and frequency with participants at study entry and subsequent visits per the SoA, Table 1.1. Participants will be trained by site personnel on:

- the signs and symptoms of hypoglycaemia, and
- treatment of hypoglycaemia.

If hypoglycaemia occurs, participants will be instructed to:

- apply the procedures for the correction of hypoglycaemia, as advised by the study site;
- have a plan in place to receive assistance and emergency treatment in case of severe hypoglycaemia;
- for any severe hypoglycaemia or concerns regarding severe hypoglycaemia, participants will be instructed to contact the study site at the earliest opportunity once the severe hypoglycaemia has resolved and the participant is safe.

The investigator or designee will review the participant data from the Glooko app and document his/her review, as per SoA (Table 1.1). Suspected or confirmed hypoglycaemia (Levels 1, 2 and 3 as described by the International Hypoglycaemia Study group 2017), and frequency of hypoglycaemia must be evaluated. Insulin dosing, dietary changes, and physical exercise (or any other contributing factor) in the development of the event should be considered. The participant

should receive additional education to mitigate the risk of hypoglycaemia, if deemed appropriate. Insulin regimen may be adjusted, and it must also be documented.

If a hypoglycaemic event meets the criteria of severe, the investigator must report it to Lilly as a serious adverse event (SAE). See Section 2.5.2 for further explanation.

2.5. Adverse Events, Serious Adverse Events, and Device Deficiencies

Appendix 2 describes the full definitions of the following events:

- Adverse Events (AEs)
- Serious Adverse Events (SAEs), and
- Device Deficiencies (DD).

These events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative) after informed consent is signed and through the safety follow-up.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet these definitions and remain responsible for following up events that:

- are serious
- are considered related to the study intervention or study procedures, or
- that caused the participant to discontinue from the study (see Section 7).

Care will be taken not to introduce bias when detecting events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about event occurrences, where possible.

After the initial report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until:

- resolution
- stabilization
- the event is otherwise explained, or
- the participant is lost to follow-up (as defined in Section 7.2.3).

For DDs, the investigator is responsible for ensuring that follow-up includes any supplemental investigations, as indicated to elucidate the nature and/or causality of any DDs. Further information on follow-up procedures is provided in Appendix 2.

The following events are considered reportable events in accordance with MDR Art. 80(2) and MDCG 2020-10/1:

a) any serious adverse event that has a causal relationship with the investigational device, the comparator or the investigation procedure or where such causal relationship is reasonably possible;

b) any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate;
c) any new findings in relation to any event referred to in points a) and b).

Table 2.1 describes the timing, deadlines, and mechanism for collecting events.

Table 2.1. Event Collection

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Adverse Events					
AE	Signing of the ICF	Participation in study has ended	As soon as possible upon site awareness	AE eCRF	N/A
Serious Adverse Events					
SAEs and SAE updates – prior to start of study intervention and deemed reasonably possibly related with study procedures	Signing of the ICF	Participation in study has ended	Within 24 hours of awareness	SAE eCRF	SAE paper form
SAEs* and SAE updates	Signing of the ICF	Participation in study has ended	Within 24 hours of awareness	SAE eCRF	SAE paper form
SAEs* – after participant's study participation has ended and the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A
Pregnancy					
Pregnancy in female participants and female partners of male participants	Signing of CRF	Participation in study has ended	Within 24 hours (See Section 2.5.2.2)	SAE eCRF	SAE paper form
Device Deficiency					
DD associated with an SAE or might have led to an SAE	Start of study intervention	End-of-study intervention	Within 24 hours of awareness	DD paper form	DD paper form
DD not associated with an SAE	Start of study intervention	End-of-study intervention	Within 1 business day of awareness	DD paper form	DD paper form
Updated DD Information	—	—	As soon as possible upon site awareness	DD paper form	DD paper form
DD (if the investigator becomes aware)	Participation in study has ended	N/A	Promptly	DD paper form	DD paper form

Abbreviations: AE = adverse event; eCRF = electronic case report form; ICF = informed consent form; N/A = not applicable; DD = device deficiency; SAE = serious adverse event.

* Serious adverse events are reported regardless of investigator's opinion of relatedness.

2.5.1. *Adverse Events*

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the insulin or study device.

An adverse device effect (ADE) is defined as an AE related to the use of a medical device. This definition includes any AEs resulting from a device deficiency, such as insufficient or inadequate IFU, deployment, implantation, installation, or operation; any malfunction of the medical device as well as any event resulting from use error or from intentional misuse of the medical device.

After the informed consent form (ICF) is signed, site personnel will record the occurrence and nature of each participant's pre-existing conditions via the eCRF, including clinically significant signs and symptoms of the disease under treatment in the study.

Pre-existing conditions, anticipated disease progression, planned surgeries, and planned interventions will only be recorded as AEs if there is a change in or worsening of medical conditions during the course of the study. Any new conditions will be recorded as AEs.

All AEs shall be reported to the Sponsor as soon as possible upon site awareness via electronic case report form (eCRF). For additional details on AEs reporting requirements please refer to Appendix 2.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to the insulin, study device, or a study procedure, considering the disease, concomitant treatment, or pathologies. A "reasonable possibility" means that there is a cause-and-effect relationship between the drug, device, or study procedure and the AE. The investigator answers "yes" or "no" when making this assessment.

The following shall be recorded/documented for each AE:

- date of the AE
- event treatment and resolution
- event severity (mild, moderate, severe)
- potential relatedness to drug, device, or study procedures, and
- determination of SAE.

Note: Participants will be instructed to report AEs that occur by calling the designated personnel at the study site as soon as possible.

The investigator is responsible for reporting applicable AEs to the ethics committee (EC), as required.

2.5.2. *Serious Adverse Events*

An SAE is defined as any adverse event that led to any of the following:

a. death,
b. serious deterioration in the health of the subject, that resulted in any of the following:
    i. life-threatening illness or injury,
    ii. permanent impairment of a body structure or a body function,
    iii. hospitalisation or prolongation of patient hospitalisation,
    iv. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
    v. chronic disease,

c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect

All SAEs shall be reported to the Sponsor within 24 hours of site awareness via eCRF.

For additional details on SAEs reporting requirements please refer to Appendix 2.

2.5.2.1. Severe Hypoglycaemia

Severe hypoglycaemic events (Level 3) must be reported to the Sponsor as an SAE.

Severe hypoglycaemia is an episode with severe cognitive impairment requiring external assistance for recovery. Severe hypoglycaemia requires another person to actively administer carbohydrate, glucagon, or other resuscitative actions. During these episodes, the participant has an altered mental status and cannot assist in his/her care, is semiconscious or unconscious, or experienced coma, with or without seizures. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. The determination of severe hypoglycaemia is made by the investigator, based upon the clinical definition, including requirement for assistance, and is not predicated on the report of a participant simply having received assistance.

2.5.2.2. Pregnancy

Pregnancy during the Study Period does not meet the definition of an AE. However, to fulfil regulatory requirements, any pregnancy should be reported following SAE reporting via eCRF within 24 hours of learning of the pregnancy.

2.5.2.2.1. Female study participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of

pregnancy will be reported, regardless of gestational age, foetal status (presence or absence of anomalies), or indication for the procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at ≥20 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any poststudy pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the Sponsor as described in protocol Section 2.5.2. While the investigator is not obligated to actively seek this information in former study participants, he/she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study. If the participant is discontinued from the study, follow the standard discontinuation process and continue directly to the study follow-up phase. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

2.5.2.2.2. Partners of male study participants who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of gestational age, foetal status (presence or absence of anomalies) or indication for the procedure.

2.5.3. *Device Deficiency*

A device deficiency is any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer.

When the ability to use the study intervention safely is impacted, the following are also DDs:

- Deficiencies in labelling information, and
- Use errors for device due to ergonomic design elements of the product.

Device deficiencies related to study interventions used in clinical trials are collected to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.

Investigators will instruct participants to contact the site as soon as possible if he/she has a DD or problem with the study intervention, so that the situation can be assessed.

An event may meet the definition of both a DD and an AE/SAE. In such cases, it should be reported as both a DD and as an AE/SAE.

The following shall be recorded/documented for each DD:

- date of complaint
- description of the complaint, and
- any associated AE(s), if applicable.

A DD may occur independently from an AE or along with an AE.

Device deficiencies shall be reported to the Sponsor or device manufacturer in accordance with provided site instructions.

Device deficiencies associated with the commercially available Dexcom G6 CGM shall be reported to the manufacturer as per product label by the investigator.

Troubleshooting of technology or connectivity may be performed prior to determination of a DD. Additional issue resolution instruction and complaint identification guidelines can be found in the Sponsor-provided training materials.

Note: Participants will be instructed to report DDs that occur during the study by calling the designated personnel at the study site as soon as possible. The site personnel must comply with the reporting obligations in this section.

For additional details on DDs please refer to Appendix 2.

2.6. Unanticipated Adverse Device Effects

A unanticipated adverse device effect (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.

3. Objectives and Endpoints

Table 3.1 outlines the objectives and endpoints for the study.

Table 3.1. Objectives and Endpoints

Objectives	Endpoints
Primary: To compare the number of MBDs during the Study Period 2 (Weeks 15 to 18), compared to the Study Period 1 (Weeks 5 and 6) in participants using the • Tempo Pen • Tempo Smart Button • Glooko RMA, and • Dexcom G6 CGM.	Primary: Difference in the average number of MBDs per week in the masked versus unmasked portions of the study. *Missed bolus dose 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 was 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: 1) To evaluate difference in participant CGM TIR (≥70 to 180 mg/dL) in the Study Period 1 versus Study Period 2. 2) To evaluate difference in participant CGM TAR (>180 mg/dL and >250 mg/dL) in the Study Period 1 versus Study Period 2. 3) To evaluate difference in participant CGM TBR (54 mg/dL ≤ TBR < 70 mg/dL and < 54 mg/dL) in the Study Period 1 versus Study Period 2. 4) To evaluate Coefficient of Variation and mean sensor glucose from of CGM values 5) To examine occurrence and change of mistimed boluses between Study Period 1 versus Study Period 2. 6) To evaluate the change in total insulin doses (basal, mealtime per meal type, correction bolus) between Study Period 1 versus Study Period 2. 7) To evaluate occurrence, change, and Study Period 1 versus Study Period 2 change in correction boluses 8) To examine the association between MBD and TIR, TAR, TBR, HbA1c 9) To examine the association between mistimed bolus and TIR, TAR, TBR, HbA1c 10) To assess device preference, satisfaction, convenience and ease of use.	Secondary: 1) CGM TIR (≥70 to 180 mg/dL) in the masked versus unmasked portions of the study. 2) CGM TAR (>180 mg/dL and >250 mg/dL) in the masked versus unmasked portions of the study. 3) CGM TBR (54 mg/dL ≤ TBR < 70 mg/dL and < 54 mg/dL) in the masked versus unmasked portions of the study. 4) Coefficient of variation and mean sensor glucose from CGM data collected from each participant 5) Occurrence and change of mistimed boluses 6) Total insulin dose per day, basal dose and insulin dose per type of meal (B, L, snacks, D) as well as corrections doses. 7) Occurrence, change, and masked versus unmasked change in correction boluses 8) CGM curves integrated with data received from the Tempo Pen 9) CGM curves integrated with data received from the Tempo Pen 10) Participant and HCP questionnaires

Exploratory: 1) To evaluate change in HbA1c from baseline to Visit 7 2) To evaluate change in HCP views on a connected diabetes management platform 3) To evaluate change in participant views on a connected diabetes management platform 4) To carry out analysis for calculation of MBDs 5) To determine participant interaction with the mobile app and its correlation with MBD change between Study Period 1 versus Study Period 2 6) To determine participant CGM wear time and correlation with MBD change between Study Period 1 versus Study Period 2 7) To evaluate participant's fear of hypoglycaemia and its correlation with MBD 8) To evaluate day and night time CGM profiles during the two periods.	Exploratory: 1) Summary statistics of actual and change in HbA1c between baseline and Visit 7 2) Outcome of IORW HCP questionnaires 3) Outcome of IORW participant questionnaires 4) CGM curves integrated with data received from the Tempo Pen/Smart Button 5) Glooko Mobile App data (e.g., number of connections to the app, number of uploads from CGM, number of CCI data uploads, % of CGM data available, number of insulin data available) and comparison of Study Period 1 and Study Period 2 app use 6) Summary of CGM wear time data and correlation with MBD data and differences between Study Period 1 versus Study Period 2 7) HFS-SF questionnaire score between Visit 1 and Visit 7 and MBD data. 8) Summarize nighttime (00:00 AM to 06:00 AM) and daytime CGM profiles during the masked/ unmasked periods.

Abbreviations: B = breakfast; CGM = continuous glucose monitoring; D = dinner; HbA1c = glycated haemoglobin; HCP = healthcare professional; IORW = Study F3Z-MC-IORW; L = lunch; MBD = missed bolus dose; MDSW = medical device software; TAR = time above range; TBR = time below range; TIR = time-in-range.

4. Study Design

4.1. Overall Design

Study IORW is a multicentre, open-label, controlled, single-arm, pragmatic outpatient study in participants with T1D or T2D that comprises 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 Glooko RMA and is unmasked to the HCP using 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 Glooko RMA and the HCP using Glooko HCP platform.

Study IORW will be carried out in France and will include 9 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 enrol a participant ratio of 4:1 for participants with T1D to participants with T2D.

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

Following screening, the participants who meet study criteria will:

- receive Sponsor-provided Humalog Tempo Pen and Tempo Smart Button, Dexcom G6 CGM, 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 HCP platform. They will also be allowed to track the basal insulin time and dosing and other data (e.g., meals, exercise) manually in the RMA. Baseline (Visit 1 and Visit 3) study questionnaires will also be completed (Table 1.1).

Participants will be asked to follow their pre-study insulin regimen (as prescribed by the investigators), lifestyle and behaviour. The study participant and HCP will not communicate, outside of the scheduled visit and activities described in Table 1.1, except in cases of acute complication, AE and 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 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 report, including insulin dose adjustments and other advices deemed appropriate (e.g., missing bolus doses, late injection timing, carb counting).

4.1.2. *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 the HCP in Glooko RMA and HCP platform. Throughout the entire Study Period 2, data from Humalog Tempo Pen/Smart Button CCI will be transferred to the Glooko RMA. Participants should continue to periodically upload Dexcom G6 CGM during Study Period 2.

Healthcare professionals 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 Glooko RMA. It is recommended that the site does not interact with the participant with respect to their Glooko RMA data during the masked Study Period 1 unless required for participant safety.

See Figure 1.1 for an overview of the study design and Section 6 for more information about the study interventions.

4.1.3. *Safety Follow-up*

Following completion of Study Period 2, study participants will complete their safety follow-up period (Table 1.1).

4.2. Visit Overview

For a quick reference to activities required at each visit, please refer to the SoA (Table 1.1).

4.2.1. *Administration of HCP Questionnaires*

The **IORW Initial HCP Questionnaire** will be completed by the physician and study coordinator/ nurse prior to FPV at the site.

The **IORW End-of-study HCP Questionnaire** will be completed by the physician and study coordinator/nurse after all participants at the site complete Visit 8 (V8).

4.2.2. *Visit 1 – Participant Screening and Enrolment*

Study participants must give written consent (signed and dated) using the ICF approved by the Sponsor (or its designee) and the governing EC.

This consent is required before any screening assessments are performed and before being allowed to participate in the study.

After an ICF is obtained, participants will commence to study screening.

4.2.2.1. Screening

Study Investigator(s), or qualified designees, will review the participant's medical records and/or history and perform assessments to determine if the participant meets all inclusion and no exclusion criteria to qualify for participation in the study (see Section 5). This includes:

- point-of-care HbA1c measurement, and
- point-of-care urine pregnancy test in women of childbearing age.

Individuals who do not meet the criteria for participation in this study must be screen failed at Visit 1 and may be rescreened (see Section 5.4).

4.2.2.2. Enrolment

If the participant meets all inclusion criteria and no exclusion criteria, they will be enrolled into the study. Study Investigator(s), or qualified designees, will review the participant's medical records and/or history and perform the required study assessments. This includes:

- medical history (including duration of disease)
- current medications
- demographics (excluding ethnicity information)
- physical examination
- vital signs (blood pressure, heart rate, respiration rate, temperature)
- HbA1c
- height, and
- weight.

The nature of any conditions that are present at the time of the physical examination and any pre-existing conditions will be documented.

For a complete list of all required assessments, please refer to the SoA (Table 1.1).

Participants previously on non-Humalog insulin will be transitioned to Sponsor-provided Humalog Tempo Pen(s) at doses similar to their current regimen and in accordance with product labelling. All participants including those who were not previously using the Dexcom G6 system will be provided with a study CGM.

This study is not designed as a titration study, but insulin doses may be adjusted to avoid hypoglycaemia or unacceptable hyperglycaemia in the opinion of the HCP.

The site will complete the following activities at Visit 1:

- administer the **IORW Participant Visit 1 Questionnaire and HFS-SF questionnaire** before the Tempo Pen/Smart Button and Glooko RMA is demonstrated
- dispense Humalog Tempo Pen(s)
- dispense Tempo Smart Button(s), and
- provide study CGM and study phone to participants.

The site will guide the participants and document Tempo Pen/Smart Button, Dexcom G6 CGM, and Glooko RMA initialisation activities, including review of the Participant Instructions handout with participants, RMA set-up, correct provision of all required participant information in the RMA. The study site will train the participant in the use of study platform components, review the functioning, understanding, and use of the study platform components and answer any questions relating to the use of the Tempo Pen/Smart Button, Dexcom G6 CGM, and Glooko RMA prior to concluding the visit. Participants will receive guidance from the study team on the use of the real time CGM data on the receiver to help them manage their diabetes and insulin dosing.

Participants will be instructed not to use the Glooko RMA "reminder" feature during study period 1.

Site personnel will review hypoglycaemia management and provide appropriate training to participants (see Section 2.4.3.1).

For a complete list of all required activities, please refer to the SoA (Table 1.1).

4.2.3. *Visit 2 – Remote Check-in 1*

Visit 2 will be conducted approximately 1 week after Visit 1. Site will perform a remote check-in in which they will review the understanding and use of the study components with participants.

During the visit, the site staff will:

- collect DDs
- collect AEs
- review concomitant medications/changes in medications
- review the functioning, understanding, and use of the study platform components, and
- confirm up-to-date participant CGM and Tempo Pen/Smart Button data was uploaded to the RMA

For a complete list of all required activities, please refer to the SoA (Table 1.1).

4.2.4. *Visit 3 – In-Person Check-in 1*

Visit 3 will be conducted approximately 5 weeks after Visit 2.

At Visit 3, the participant will be required to visit the study site with his/her:

- mobile device with RMA
- CGM
- Dexcom receiver
- Tempo Pen(s) currently in use, and
- Tempo Smart Button.

Unused Tempo Pen(s) may remain at the participant's residence so long as he/she checks how much is remaining to aid in resupply calculations.

During the visit, the site staff will:

- collect DDs
- collect AEs
- review concomitant medications/changes in medications
- review study supplies and dispense, as needed
- review the functioning, understanding, and use of the study platform components
- confirm up-to-date participant CGM data was uploaded to the RMA
- administer **IORW Participant V3 Questionnaire**
- administer **HFS-SF Questionnaire**, and
- weigh the participant.

For a complete list of all required activities, please refer to the SoA (Table 1.1).

In addition, following completion of the **IORW Participant Visit 3 Questionnaire and HFS-SF Questionnaire**, the site staff will unmask the CCI [redacted] data, review the participants' dosing patterns, and discuss information from the HCP Portal with the participant about his/her dosing habits and glucose control collected during Study Period 1.

To accomplish this:

- HCPs will be able to display Study Period 1 data on the HCP Portal which will contain previously participant-masked information about insulin dosing and glycaemic status
- the investigator or designee will review Study Period 1 data
- the investigator or designee will share and discuss the data collected during Study Period 1 with the study participant
- dose adjustments and other advices provided by the HCP will be recorded, and
- any educational activities that would result from the review of the report would be documented by the HCP.

4.2.5. *Visit 4 – Remote Check-in 2*

Visit 4 will occur approximately 1 week after Visit 3. At Visit 4, site staff will perform a remote check-in during which they will review the understanding and use of the study components with participants.

During the visit, the site staff will:

- collect DDs
- collect AEs
- confirm up-to-date participant CGM and Tempo Pen/Smart Button data was uploaded to the RMA
- review concomitant medications/changes in medications, and
- review the functioning, understanding, and use of the study platform components.

For a complete list of all required activities, please refer to the SoA (Table 1.1).

4.2.6. *Visit 5 and 6 – Remote Check-in 3 & 4*

Visit 5 will occur approximately 3 weeks after Visit 4.

Visit 6 will occur approximately 4 weeks after Visit 5.

Site staff will perform a remote check-in with the participant during which they will:

- collect DDs
- collect AEs
- review concomitant medications/changes in medications
- review the functioning, understanding, and use of the study platform components (if deemed necessary based on previous visits)
- confirm up-to-date participant CGM and Tempo Pen/Smart Button data was uploaded to the RMA
- share and discuss glucose control and insulin dosing habits (adjust the dose if appropriate) with the participant (from last data review, i.e., approximately 4 weeks)
- document any educational activities that would result from the review of the report by the HCP, and
- review study supplies status.

For a complete list of all required activities, please refer to the SoA (Table 1.1).

4.2.7. *Visit 7 – In-Person Check-in 2*

Visit 7 will occur approximately 4 weeks after Visit 6.

At Visit 7, the participant will be required to visit the study site and bring his/her:

- mobile device with RMA
- CGM
- Dexcom receiver
- Tempo Pen(s) currently in use
- unused Humalog Tempo Pen(s), and
- Tempo Smart Button.

Participants will return all appropriate Sponsor-provided study materials as per Sponsor instructions.

During the visit, the site staff will:

- collect DDs
- collect AEs
- review concomitant medications/changes in medications

- confirm up-to-date participant CGM and Tempo Smart Button data was uploaded to the RMA and
- review and discuss glucose control and insulin dosing habits (since last visit, i.e., approximately 4 weeks) with the participant, using the HCP Portal information.

The site will also perform the following assessments:

- weight, and
- point-of-care HbA1c measurement.

In addition, following review of the summary on Glooko HCP platform and discussion with the participant, the site staff will administer the **IORW Participant Visit 7 Questionnaire and HFS-SF Questionnaire** to the participant.

After Visit 7 is complete, participants will transition to a non-study insulin regimen and a non-study CGM device (if applicable).

For a complete list of all required activities, please refer to the SoA (Table 1.1).

4.2.8. *Visit 8 – Safety Follow-up and Study Exit*

Approximately 3 days after participants have stopped the study intervention (Visit 7), the study site will contact the participant via a phone call to:

- review AEs and DDs,
- review concomitant medications/changes in medications following the transition to non-study insulin regimen and a non-study CGM device (if applicable), and
- note that study participation ends at completion of this phone visit.

For a complete list of all required activities, please refer to the SoA (Table 1.1).

4.2.9. *Unscheduled Visits*

At any time, the participant may request an unscheduled site visit, either in-person or remotely. During an unscheduled visit, the site may triage any issues with the study platform and/or refill the participant's supplies.

During any unscheduled visit, site staff will:

- collect DDs
- collect AEs
- review concomitant medications/changes in medications
- review the functioning, understanding, and use of the study platform components (if deemed necessary based on previous visits), and
- review study supplies and dispense as needed.

For a complete list of all required activities, please refer to the SoA (Table 1.1).

4.3. Early Discontinuation Visits

Participants discontinuing from the study prematurely, for any reason, should return to the study site.

The participant will be required to bring his/her:

- mobile device with RMA
- CGM
- Dexcom receiver
- Tempo Pen(s) currently in use
- unused Tempo Pen(s), and
- Tempo Smart Button.

Participants will return all appropriate Sponsor-provided study materials as per Sponsor instructions.

During the visit, the site personnel will:

- collect DDs
- collect AEs
- review concomitant medications/changes in medications
- confirm up-to-date participant CGM and Tempo Smart Button data was uploaded to the RMA, and
- review and discuss glucose control and insulin dosing habits (adjust the dose if appropriate) with the participant, using the Glooko HCP Portal information.

The site will also perform the following assessments:

- weight, and
- point-of-care HbA1c measurement.

In addition, following review of Glooko summary report and discussion with the participant , the site staff will administer to the participant:

- the IORW Participant **Visit 3** Questionnaire and HFS-SF Questionnaire if the Early Termination visit takes place before Visit 3,
- the IORW participant **Visit 7** Questionnaire and HFS-SF Questionnaire if if the Early Termination visit takes place after Visit 3.

For a complete list of all required activities, please refer to the SoA (Table 1.1).

Site personnel should document details regarding the reason for discontinuation, if possible (see Section 7). Study participants will transition back to their non-study insulin (if applicable) and their non-study CGM devices (if applicable).

4.4. Scientific Rationale for Study Design

4.4.1. *Rationale for Investigation of Missed Bolus Dose*

This study objectively estimates:

- MBDs and their relationship to short-term glycaemic control are clinically relevant, and
- participant behaviour and satisfaction among participants.

The Tempo Pen/Smart Button allows for objective collection of data that can be assessed as missed, mistimed, or suboptimal CCI . Prior to a downloadable CCI data, other HCPs have collected bolus data for multiple daily injection subjectively from participants' paper or electronic diaries.

There is no standard-of-care or comparator arm because the primary objective of this study is to objectively estimate MBDs from reliable automated collection, which can only happen if the participant uses a smart insulin pen recording the injections. Therefore, the last 2 weeks of Study Period 1 (Week 5 to Week 6 [Visit 3]) will be used for analyses with masked RMA as baseline data.

The study duration of 18 weeks (6 weeks +12 weeks) is long enough for the assessment of MBDs in a study setting. Each enrolled participant must be on a mealtime bolus insulin regimen with at least 3 or more bolus doses daily (Section 5.1).

4.4.2. *Rationale for Single-Arm Study*

A single-arm clinical study that is statistically powered to detect a difference (see Section 9) would provide reliable evidence to study hypothesis where participants can be their own control. This would allow to see the benefit of unmasking the RMA and connected pen while adjusting for participants' dosing behaviour at baseline.

The masked period will run for a duration of 6 weeks to allow participants 4 weeks to adjust from another rapid acting insulin analogue to Humalog, to start using Glooko RMA and Dexcom G6 CGM (if not already using it) and provide sufficient and reliable data for their baseline (last 2 weeks of Study Period 1).

The unmasked period will run for a duration of 12 weeks to allow the participant to use the data CCI on the RMA and use this information during the HCP interaction.

4.4.3. *Rationale for Inclusion of Predominately Participants with Type 1 Diabetes*

Adult populations with T1D and T2D on basal bolus were chosen to participate as both can be treated with prandial insulin and use a connected pen with an RMA.

The IORW study plans to recruit predominantly participants with T1D on basal bolus who have uncontrolled diabetes (defined as HbA1c ≥8%) because most of them are already on CGM and being a younger population, they are accustomed to the use of various medical application for the daily management of their diabetes.

Furthermore, there are limited data regarding MBDs in patients with T2D on basal bolus. Therefore, we based our power calculation on data available for patients with T1D and plan to:

- gather data for a limited number of participants with T2D, and
- focus this study predominantly on those with T1D.

4.5. End-of-Study Definition

End-of-study is the date of the last visit (Visit 8) shown in the SoA (Table 1.1) for the last study participant.

No intervention is allowed following the end of the trial.

4.6. Travel Restriction Flexibilities

Appendix 4 describes alternative approaches to study activities, should the site or participants encounter national-, local-, or business-imposed travel restrictions, where travel to sites or in-person interactions would be ill-advised or restricted.

It is the responsibility of the Investigator to assess this situation at the site and provide real time feedback to Sponsor or Sponsor representative if:

- there is the potential to impact clinical research operations, or
- conditions at the site have the potential to impact the ability to monitor either the safety of participants or the scientific integrity of study.

This includes reporting any disruptions that arise:

- directly if the site is impacted by COVID-19, or
- indirectly as the result of disruptions in travel networks, quarantines, or other social distancing mandates.

5. Study Population

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

5.1. Inclusion Criteria

Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Participants are eligible to be included in the study only if they meet all of the following criteria at enrolment:

[1] Have been diagnosed (clinically) with T1D for at least 1 year or are patients with T2D on basal bolus insulin therapy for at least 6 months

[2] Capable of giving signed informed consent, including compliance with the requirements and restrictions listed in the ICF and in this protocol

[3] Men or women of age ≥18 years

[4] HbA1c ≥8% as confirmed by point-of-care test at screening

[5] Are currently using CGM and agree to use the Dexcom G6 and Glooko RMA during the study.

[6] Are currently using Humalog ® insulin or another rapid acting insulin analogue (e.g., Apidra®, or Novorapid®) and agree to switch to study-provided Humalog mealtime insulin for duration of trial

[7] Have been prescribed ≥3 doses of bolus insulin per day

[8] Must be taking a stable insulin dose regimen (per investigator's judgement) for at least 3 months preceding study screening

[9] Have sufficient ability, in the opinion of the investigator, to communicate in the French language to perform study activities and comply with study requirements

[10] Have no physical or cognitive disabilities that would, in the opinion of the investigator, preclude participant from using Glooko RMA for study activities and comply with study requirements

[11] Have in-home refrigeration for storage of insulin

[12] Female participants of childbearing potential:

i. cannot be breastfeeding, pregnant or intend to become pregnant during the trial period

ii. must:

- remain abstinent, or
- use 1 highly effective method (<1% failure rate) of contraception or a combination of 2 effective methods of contraception, consistent with local regulations, for the entirety of the study (see Appendix 3), and

iii. test negative for pregnancy based on a urine pregnancy test at Visit 1. Additional local urine pregnancy tests may be conducted for duration of trial at discretion of investigator.

5.2. Exclusion Criteria

Participants will be excluded from study enrolment if they meet any of the following criteria:

[13] Previously used the Glooko RMA and/or Dexcom G6 CGM and were judged by the investigator to be non-adherent

[14] 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

[15] 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

[16] Have previously used or have been using an approved or investigational connected pen platform within the 3 months prior to screening

[17] Are currently pregnant or plan to become pregnant during the next 4-6 months

[18] Are on ultra-rapid insulin (e.g., Fiasp or Lyumjev) or rapid acting human insulin (i.e., Humulin) for previous 3 months, at the time of screening

[19] Have any hypersensitivity or allergy to any of the insulins or excipients used in this trial

[20] Use of corticosteroid therapy for more than 10 days within the 3 past months, or patient who ought to be treated by corticosteroid during the Study Period

[21] Are currently undergoing dialysis treatment or have any other medical condition which may preclude them from participating in this trial as per the investigator's judgement

[22] Have vision loss or vision impairment that does not allow recognition of Glooko RMA screen features

[23] Have impaired dexterity which limits ability to use the RMA

[24] Have previously completed or withdrawn from this study

[25] 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

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

5.3. Lifestyle Restrictions

Participants must have a stable lifestyle with no changes to dietary or exercise habits during the course of the study, with the exception of those advised by the investigator as part of the Study Period 2.

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes:

- demography (excluding ethnicity)
- screen failure details
- eligibility criteria, and
- any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened no earlier than after 1 month from the initial screen if study enrolment is still ongoing.

6. Study Intervention and Concomitant Therapy

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to/used by a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

This study involves a treatment of study participants with marketed insulin lispro (Humalog 100 units/mL), at doses as prescribed by HCP, administered via the Humalog Tempo Pen (provided by the Sponsor).

The Tempo Smart Button, (provided by the Sponsor) will be used to detect, store, and transfer insulin dose-related data from a Tempo Pen to Glooko RMA.

The Tempo Smart Button is hand-held and surface-contacting with intact skin only (Table 6.1). No participant contact components are in contact with the drug product. The user prepares the Smart Button for use by attaching it to the dose knob of a Tempo Pen prefilled insulin pen. With the Smart Button attached, the user administers a dose from the Tempo Pen. The doses will be administered according to the participant's usual practices.

Table 6.1 shows the study platform components that will contact the participants body, either on the surface or subcutaneously.

Table 6.1. Study Platform Components that Contact the Body

Study Platform Component	Contact Area of Human Body
Tempo Smart Button	Hand
Dexcom G6 Sensor	Subcutaneously at: • back of upper arm, or • belly
Dexcom G6 Transmitter	Back of upper arm or belly
Dexcom G6 Applicator	Back of upper arm or belly
Dexcom Receiver	Hand
Tempo Pen	Subcutaneously at: • stomach area, • buttocks, • upper legs, or • upper arms.

HCP prescribed insulin dosage modifications should not occur during Study Period 1, apart from acute complication or to prevent severe hypoglycaemia or hyperglycaemia, occurring during that Study Period. During Study Period 2, insulin adjustments are allowed based on the investigator's medical judgement using the available glucose and insulin data.

All study participants including those who were not previously using the Dexcom G6 system will be provided with a study CGM and will agree to start using the Dexcom G6 if they were on a different CGM pre-study. All Dexcom G6 users will need to have their receiver within a 6-metre range of the transmitter to collect study data.

Data from Humalog Tempo Pen/Smart Button and Dexcom G6 will be uploaded to the Glooko RMA/receiver throughout the study.

The study platform set-up and appropriate training will be provided to all study participants by study site personnel at Visit 1. Appropriate instructions for use will also be provided to participants as part of the participant's study information package.

Study participants will continue their pre-study concomitant anti-hyperglycaemic medication and basal insulin therapies (Table 6.3).

Table 6.2 shows the treatment regimens for each Study Period.

Table 6.2. Treatment Regimens for Each Study Period

Study Period 1	**Study Period 2**
Humalog (doses as prescribed by HCP) administered via Tempo Pen	Humalog (doses as prescribed by HCP) administered via Tempo Pen
Tempo Smart Button	Tempo Smart Button
Dexcom G6 CGM	Dexcom G6 CGM
Glooko RMA and Glooko HCP platform (CCI [redacted] data masked on RMA and unmasked on HCP platform)	Glooko RMA and Glooko HCP platform (CCI [redacted] data unmasked)

Abbreviations: HCP = healthcare professional; CGM = continuous glucose monitor; RMA = research mobile application.

All devices used in this study (Tempo Smart Button, Dexcom G6, Glooko MDSW) will be used within their intended use and indications for use. All medicinal products used in this (Humalog Tempo Pen) are European Medicine- (EMA-) approved and will be used within their marketed intended use and indications for use.

Detailed description of technical and functional features of the study platform components are outlined in Section 2.3.

6.2. Preparation, Handling, Storage, Labelling and Accountability

- Study platform components will be labelled according to applicable regulatory requirements.
- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

- Only participants enrolled in the study may receive study intervention and only authorised site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised study personnel.
- The insulins must be stored at the study site under refrigerated conditions (between 2°C and 8°C) in a locked and secure place. Insulin must not be frozen.

Detailed information on storage requirements for the study products is provided in Tempo Smart Button IFU and Humalog Package Insert.

The investigator or authorised study personnel are responsible for product accountability, reconciliation, and record maintenance of study products (that is, receipt, reconciliation, and final disposition records). Traceability for all dispensed study products will be documented throughout the course of the trial in the eCRF utilising lot and/or serial numbers and detailed information about this process will be available as part of site's training materials.

6.3. Measures to Minimise Bias

This is an open-label, single-arm, pragmatic study in which all study participants will be receiving insulin lispro 100 units/mL (Humalog) via Tempo Pen. Study participants and study personnel will not be blinded to insulin treatment or study devices. Study participants who meet all inclusion/ exclusion criteria (Sections 5.1 and 5.2) will be enrolled into the study at Visit 1 (Week 0).

To minimise the bias, study participants will be used as their own control by designing the study to include two study periods: Study Period 1 (run-in) and Study Period 2 (intervention). During Study Period 1, CCI dosing and timing data in Glooko RMA will be masked to study participants and no dosage modifications will occur during Study Period 1, apart from acute complication occurring during that Study Period. Study participants will only be unmasked to the CCI dosing and timing data in Glooko RMA during Study Period 2. Study personnel will be unmasked during both Study Period 1 and Study Period 2.

Study questionnaires will also be administered at multiple time points (Visit 1, Visit 3, and Visit 7) to provide baseline and endpoint data.

Additionally, the study will be conducted with participants in an outpatient setting with study interventions representative of standard clinical practices, to minimise bias associated with participation in a clinical trial.

6.4. Continued Access to Study Intervention After the End of the Study

No intervention is allowed following the end of the trial. Participants will be allowed to continue with commercially available insulin products and devices if they wish.

6.5. Treatment of Overdose

Excess insulin administration may cause hypoglycaemia and hypokalaemia. Mild episodes of hypoglycaemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous or nasal glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery. Hypokalaemia must be corrected appropriately.

In the event of an overdose, the investigator should:

- Refer to Humalog Tempo Pen Package Insert
- Contact the medical monitor immediately
- Evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced, and
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until hypoglycaemia is corrected.

6.6. Concomitant Therapy

Table 6.3 summarises the medications that would and would not exclude participants from the study.

Table 6.3. Summary of Concomitant Therapies that Are Permitted and Not Permitted during the Study

Medications	T1D participants	T2D participants
Insulin degludec (U-100 or U-200), insulin detemir (U-100), insulin NPH, insulin glargine (U-100 and U-300)	Allowed	Allowed
Insulin glulisine, insulin aspart, or human R insulin	Not allowed[a]	Not allowed[a]
Insulin lispro in any device other than study-provided pens	Not allowed[a]	Not allowed[a]
Pre-mixed insulin	Not allowed	Not allowed
Sulfonylureas, meglitinides, alpha-glucosidase inhibitors	Not allowed	Allowed as prescribed by the physician
Metformin, DPP-4 inhibitors, SGLT-2 inhibitors, GLP-1 RA (oral or injectable),	Not allowed	Allowed
Corticosteroids	Not allowed[b]	Not allowed[b]

Abbreviations: DPP = Dipeptidyl peptidase; GLP-1 RA = Glucagon-Like Peptide-1 Receptor agonist; NPH = Neutral Protamine Hagedorn; SGLT2 = Sodium-glucose co-transporter-2

[a] Not allowed unless due to emergency circumstances or factors that requires non-study insulin use and duration must not exceed ≥8 days.

[b] Not allowed unless due to emergency circumstances or factors that require corticosteroids use and duration must not exceed ≥8 days.

Participants are allowed to use oral diabetes medications that are being used on-label. Any changes to non-insulin diabetes medication use during the study should not take place unless medically indicated (e.g., hypoglycaemic event); any such changes must be recorded.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

7.1. Discontinuation of the Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will not remain in the study to be evaluated. Participants should report AEs and DDs and complete other safety follow-up at exit visit, in accordance with this protocol. Safety follow-up should be performed as outlined in Section 1.3 (SoA), and Section 2.5 (AEs and SAEs of the protocol).

The Sponsor shall be notified of any instance of participant withdrawal or discontinuation. Any data collected up to the point of withdrawal or discontinuation may be used in the study.

See the SoA (Table 1.1) for data to be collected at the time of discontinuation of study intervention and for any further evaluations that need to be completed.

There will not be any research-related follow-up visit once their participation in the trial has ended, as the study participants will be routinely monitored as part of their diabetes management. In the event of discontinuation or early termination, participants will be contacted 3 days after they have stopped the study intervention for a remote follow-up.

7.2. Participant Discontinuation/Withdrawal from the Study

7.2.1. *Participant Withdrawal*

A participant may withdraw from the study:

- at any time at his/her own request
- at the request of his/her designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons
- if enrolment in any other clinical study involving an investigational product or enrolment in any other type of medical research judged not to be scientifically or medically compatible with this study
- if the participant needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws and regulations, or
- if the participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent.

7.2.2. *Participant Discontinuation*

Discontinuation is expected to be uncommon.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See the SoA (Table 1.1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued from both the study intervention and the study at that time.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

Participants will be discontinued in the following circumstances:

- enrolment in any other clinical study involving an investigational product or enrolment in any other type of medical research judged not to be scientifically or medically compatible with this study
- participation in the study needs to be stopped for identified medical, safety, regulatory, or other reasons consistent with applicable laws and regulations
- a participant becomes pregnant during the course of the study
- the investigator decides that the participant should be discontinued from the study
- a participant did not meet the enrolment criteria and was inadvertently enrolled, and
- the participant, the participant's designee, for example, parents or legal guardian requests to be withdrawn from the study.

If the Sponsor or investigator identifies a participant who did not meet enrolment criteria and was inadvertently enrolled, then the participant should be discontinued from study treatment, unless there are extenuating circumstances that make it medically necessary for the participant to continue on study treatment.

If the Sponsor and the investigator agree that it is medically appropriate to continue, the investigator must obtain documented approval from the Sponsor to allow the inadvertently enrolled participant to continue in the study with or without treatment with study product.

7.2.3. *Lost to Follow-Up*

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

Site personnel are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

8. Study Assessments and Procedures

Study procedures and their timing are summarised in the SoA (Table 1.1).

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Table 1.1 lists the SoA, with the study procedures and their timing (including tolerance limits for timing).

8.1. Effectiveness Assessments

8.1.1. *Primary Assessments*

The primary assessment compares the number of MBDs per week in Study Period 1 and Study Period 2 in participants with T1D or T2D using CGM measurements and CCI [redacted] data. Missed bolus doses will be determined by the glucose excursion as measured by the CGM.

Missed bolus dose (Figure 8.1) 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 was 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. 2021).

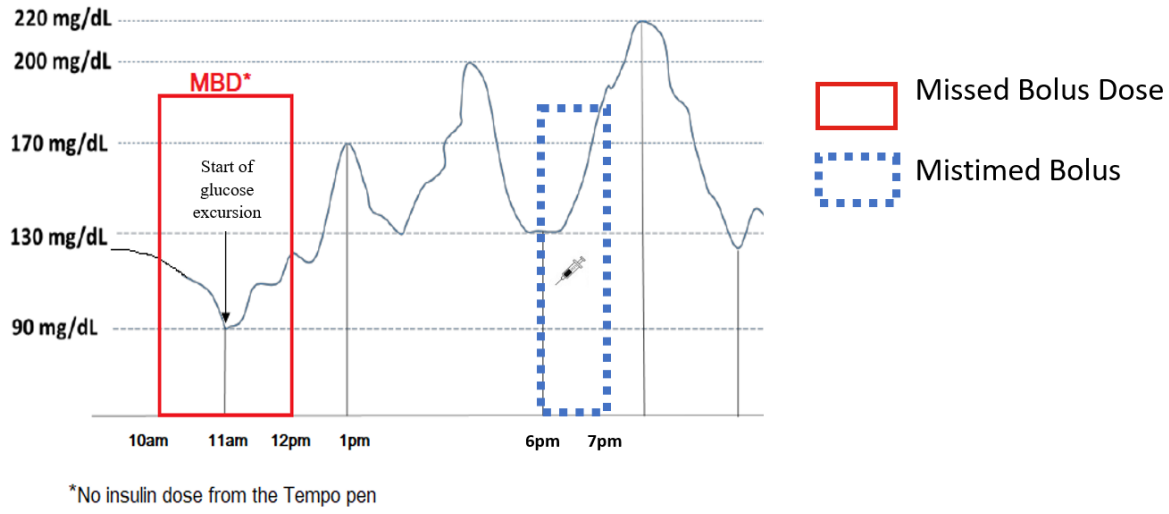


Figure 8.1. Illustration of missed bolus dose and mistimed bolus.

Using Figure 8.1 as an example, in this study:

- if a dose between 10 and 11 am would be classified as the correct or optimum time to administer the insulin dose, no insulin dose between 10 am and 12 pm would be a MBD; and
- if a dose between 5 and 6 pm would be classified as the correct or optimum time to administer the insulin dose before the meal, an insulin dose between 6 and 7 pm is defined as a mistimed bolus dose.

Sy et al. (2022) provides a graphical representation of several days of CGM data with various meal bolus situations.

8.1.2. *Secondary Assessments*

Study IORW will have secondary measures as described in Table 3.1.

The study will evaluate the change in percentage TIR, TAR, TBR, mean sensor glucose coefficient of variation between Study Period 1 and Study Period 2 in participants with T1D or T2D using CGM and CCI data. The glucose TIR for this analysis is ≥70 and ≤180 mg/dL.

In addition, the occurrence and change in mistimed bolus will be evaluated (Figure 8.1).
A mistimed bolus dose is defined as a bolus dose administered from the start of a glucose excursion (meal) up to 1 hour after the start of glucose excursion and before the peak of glucose excursion.

Change in correction boluses from masked to unmasked period will also be evaluated. Correction bolus is defined as taking a bolus dose given 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.

8.1.3. *Exploratory Assessments*

Study IORW will also have exploratory assessments:

- Sensitivity analysis for calculation of MBDs, using CGM curves integrated with the data received from the Tempo Pen/Smart Button.
- Participant interaction with the RMA based on app usage data (e.g., number of connections to the app, number of CCI data uploads, percentage of CGM data available, percentage of CCI data available) and comparison of usage in Study Period 1 and Study Period 2.
- Change in HbA1c from baseline to Visit 7.
- Understanding changes in participant views on a connected diabetes management platform.
- Understanding changes in HCP views on a connected diabetes management platform.
- Understanding the participant's fear of hypoglycaemia and correlate it with MBD.
- Understanding and summarizing the participant's day and night time CGM profiles during the two periods.

8.2. Safety Assessments

Not applicable as no clinical laboratory test are planned for this study. However, if any laboratory tests need to be performed during routine care for participant safety evaluations, it will be the responsibility of the HCP.

9. Statistical Considerations

9.1. Statistical Hypotheses

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

The primary analyses will be conducted at the end of the clinical study on data collected from all participants as described in the Sections 9.2 and 9.3.

9.2. Analyses Sets

Safety analyses will be carried out on the **Safety Population**, which consists of all participants with at least 1 measurement in the masked app period and/or unmasked app period.

Efficacy analyses will be carried out on the main analysis set. To allow for this clinical trial to be generalisable to the wider population and to prevent the chance of analysing a biased set of "only adherent" participants, efficacy analyses will be repeated on the sensitivity analysis set.

9.2.1. *Main Analysis Set*

The initial 4 weeks will allow a wider population of participants (Humalog and non-Humalog users as well as those using and not using Dexcom G6 CGM prior to study entry) to reach a routine before baseline data assessment (such as MBD, TIR, TAR, etc.) is carried out.

Unless stated otherwise, data collected from the last 2 weeks (Weeks 5 and 6) of the masked app (baseline) period and the last 4 weeks (Weeks 15 to 18) of the unmasked app period will be used to answer the primary and secondary objectives. In other words, 2 weeks prior to Visit 3 (face-to-face) and 4 weeks prior to Visit 7 (face-to-face).

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 CGM data out of the last 14 days (Weeks 5 and 6) in the masked app period will be considered as evaluable participants (Danne et al. 2017; Battelino et al. 2023).

Among these participants (as described above), only the participants that satisfy the below criteria for the unmasked app period will be considered as evaluable participants:

- with at least 20 of 28 days' worth of CGM data (Weeks 15 to 18), or
- discontinuing early that have at least 20 days' worth of CGM data in the whole unmasked app period (Weeks 7 to 18).

9.2.2. *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 app period (Weeks 1 to 6), and all participants with at least 20 days' worth of CGM data in the whole unmasked app period (Weeks 7 to 18).

9.3. Statistical Analyses

Statistical analysis of this study will be the responsibility of Lilly or its designee. Efficacy analyses will be conducted on the main and sensitivity analysis sets and safety analyses on the safety analysis set, unless stated otherwise.

The analyses for the primary endpoint and majority of the secondary endpoints (TIR, TAR, TBR, mistimed bolus, correction bolus) will be conducted using a mixed-effect models for repeated measures which will:

allow the model to adjust for key baseline characteristics (baseline HbA1c and body mass index) if appropriate, and
compare the masked app period against the unmasked app period.

Spearman rank-order correlation will be used to test the association between MBD and:

- TIR
- TAR
- TBR, and
- HbA1c.

For all statistical tests, $p \leq 0.05$ is considered statistically significant. No multiplicity adjustment will take place.

For continuous variables, descriptive statistics will entail:

- mean
- standard deviation (SD)
- minimum
- median, and
- maximum.

For categorical variables, frequency, and percentage will be obtained.

Baseline characteristics (such as type of diabetes, gender, age, duration of disease, etc.) will be summarised for all the participants entered in the trial, and for the analysis sets described above.

Where appropriate, graphs to illustrate glucose levels will be also be presented.

Amount of useable data from the CGM device and pen will be summarised for the main analysis set. The primary reasons for discontinuation will be summarised by Study Period and participant allocation will be summarised by investigative site for those who have entered the trial.

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.

9.3.1. *Primary Endpoint*

The average number of MBDs per week during the masked and unmasked app periods as well as the difference will be summarised and analysed with the model described in Section 9.3.

Table 3.1 outlines the objectives and endpoints for the study and provides the definition of MBD.

Missed bolus doses will be calculated for:

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

9.3.2. *Secondary Endpoints*

The following endpoints will be calculated and analysed with the model described in Section 9.3 for the masked and unmasked periods:

- Change in participant CGM TIR (≥70 and ≤180 mg/dL).
- Change in participant CGM TAR (>180 mg/dL and >250 mg/dL).
- Change in participant CGM TBR (<54 mg/dL and 54 mg/dL ≤ X <70 mg/dL).
- Change in mistimed bolus dose [0,1] – 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, is classified as a mistimed bolus dose. The definition of a glucose excursion remains the same for an MBD.
- Change in correction boluses - 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.
- Change in insulin doses: basal and mealtime, ratio basal/mealtime, dose per meal as well and total dose in IU/kg.
- Correlations between MBD/mistimed bolus and:
    - TIR
    - TAR
    - TBR, and
    - HbA1c.
- Other secondary analyses:
    - evaluate coefficient of variation (from CGM data)
    - evaluate mean sensor glucose (from CGM data).
- Exploratory analyses:
    - change in HbA1c from baseline (Visit 1) to Visit 7 (last visit),
    - healthcare professional questionnaires, and
    - participant questionnaires
    - day and night time CGM profiles during the two periods.

9.3.3. *Safety Analyses*

- Descriptive statistics of AEs (including the number of severe hypoglycaemic events) and Device Deficiencies (DDs) will be included and summarised.
- Discontinuations will also be summarised.

9.3.4. *Other Analyses*

Participant and HCP feedback on individual questions will be summarised using frequency and percentages. The shift of responses from masked period (Visit 1, Visit 3) to unmasked period (Visit 7) will also be summarised using shift tables.

In addition, exposure to the RMA will be summarised by period and overall.

9.3.5. *Subgroup Analyses*

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

- age group, and
- T1D or T2D.

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

9.3.6. *Sensitivity Analyses*

Sensitivity analyses will be performed for the primary endpoint. Varying definitions of MBD will be conducted as sensitivity analyses. 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.

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

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

9.4. Sample Size Determination

This clinical study aims to enroll approximately 50 participants (i.e., 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).

As this is a relatively new field with very limited data, a range of correlations and standard deviations was considered in the sample size calculation as well as varying dropout rates. Table 9.1 provides an overview of how the appropriate sample size was identified.

Table 9.1. Sample Sizes of Evaluable Participants Needed to Detect at Least a Mean Difference of 0.323 Missed Bolus Doses Per Day (Alpha=0.05, Power=80%)

Correlation	Standard deviation (SD)			
	0.4	0.419	0.5	0.6
0.2	22	24*	33	46
0.3	19	21	29	40
0.4	17	18	25	35
0.5	15	16	21	30

*Note: represents appropriate sample size identified for current study.

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

- at least 24 participants will complete the study with analysable data (see Table 9.1 and Section 9.2.1)
- scope for increased variability (up to SD of 0.5)
- for non-analysable participants due to technical problems
- 35% dropout rate was assumed based on previous study results (Adolfsson et al. 2020, Gomez-Peralta et al. 2022,) and the impact of missing CGM data which would reduce the number of evaluable patients.

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.

9.5. Interim Analyses

No interim analyses will be performed.

10. Appendices

Appendix 1. Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:
Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences International Ethical Guidelines.
Applicable International Council for Harmonisation (ICH) Good Clinical Practice Guidelines.
Applicable laws and regulations.
The protocol, protocol amendments, ICF, and other relevant documents (for example, advertisements) must be submitted to an EC by the investigator and reviewed and approved by the EC before the study is initiated.
Any amendments to the protocol will require EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

> Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:
Providing written summaries of the status of the study to the EC annually or more frequently in accordance with the requirements, policies, and procedures established by the EC.
Notifying the EC of SAEs and/or USADEs or other significant safety findings as required by EC procedures.
Providing oversight of the conduct of the study at the site and adherence to requirements of International Organisation for Standardisation (ISO) 14155, ICH guidelines, the EC, EU Regulation 2017/745 for clinical studies, and all other applicable local regulations.
Investigator sites are compensated for participation in the study as detailed in the Clinical Trial Agreement.

Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of ISO 14155, local regulations, ICH guidelines, and the EC or study site.
- The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- Participants will be informed of the emergency contact details for the principal investigator at each site.
- Participants will be informed that their personal data will be stored for up to 30 years (per sponsor record retention rules) for potential future research in the field of diabetes.
- A copy of the ICF(s) must be provided to the participant and is kept on file.

Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records, datasets, or tissue samples that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data, including the RMA data, will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for his/her data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the Sponsor, by appropriate EC members, and by inspectors from regulatory authorities.
- The Sponsor has processes in place to ensure data protection, information security and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

Dissemination of Clinical Trial Data

A CSR will be provided for this study and a summary of study information, including tabular study results, will be provided on publicly available websites as required by local law and regulation. Dissemination of study data will be performed according to all applicable Lilly and international policies.

Publication Policy

In accordance with the Sponsor's publication policy, the results of this study will be submitted for publication by a peer-reviewed journal.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (for example, data from Glooko RMA). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, EC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (for example, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (for example, contract research organisations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the Clinical Trial Agreement (CTA) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.
- In addition, the Sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by the Sponsor or its representatives, and/or regulatory agencies at any time.
- Investigators will be given notice before an audit occurs.

Deviations

- Deviation(s) from this protocol, signed agreement, applicable regulations, and any conditions of approval imposed by an EC or applicable regulators shall be documented (including date of and reason for deviation). Site personnel must identify and report deviations to the Sponsor within 5 working days.

- Under emergency circumstances, deviations from this protocol to protect the rights, safety, or well-being of participants is allowed without prior approval of Lilly and the EC. The site shall document and report these emergent deviations to Lilly and the EC within 5 working days after the emergency occurred.

- If appropriate, actions to secure compliance may be taken by Lilly. These actions may include discontinuation of device shipments, removal/disposal of devices from the investigator, or termination of an investigator's participation in the study.

Data Capture System

- The investigator is responsible for
    - the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the eCRF, and
    - ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor.
- An electronic data capture (EDC) system will be used in this study. The system is a validated and secure system, allowing only those with permission (unique to each user) to access data. The system creates a computer generated, time stamped audit trail in accordance with 21 CFR Part 11.
- The study site maintains a separate source for the data entered by the site into the Sponsor data capture system. Data will be stored in accordance with retention requirements in applicable regulations. Assessments can be directly recorded by the investigator site personnel or a delegate into the EDC. The directly entered data will serve as source documentation.
- The investigator will maintain an original, separate, written, or electronic record of any data entered to EDC system. A certified copy of the respective data entry will be downloaded by the investigator for retention.
- Data from DDs submitted to the Sponsor will be encoded and stored in the global PC management system.
- Data will be reviewed throughout the study to identify any missing data, errors in data entry, or inconsistencies in the data provided. A query process will be used to resolve any discrepancies identified during the data review process.
- Data collected via the Sponsor-provided data capture systems will be stored at third parties. The investigator will have continuous access to the data during the study and until decommissioning of the data capture systems. Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be

explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

- CCI [redacted] data (from the Tempo Pen/Tempo Smart Button) and glucose measurement data (from the CGM) transferred into the Glooko RMA or other data entered directly by the participant into RMA. In these instances where there is no prior written or electronic source data, the RMA record will serve as the source.
- Definition of what constitutes source data can be found in the Data Capture System in the previous section.

Trial and Site Start and Closure

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

- for study termination:
    - discontinuation of further study intervention development.
- for site termination:

    failure of the investigator to comply with the protocol, the requirements of the EC or local health authorities, the Sponsor's procedures, or GCP guidelines;
    inadequate recruitment (evaluated after a reasonable amount of time) of participants by the investigator; and
    total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the ECs, the regulatory authorities, and any contract research organisation(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and assures appropriate participant therapy and/or follow-up.

Investigator Information

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

A complete list of investigators, and other institutions involved in this study will be maintained by the Sponsor and updated as needed throughout the study. A list of all participating investigators in the trial will be provided to each study site and EC in a separate document.

Appendix 2. Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

The definitions and procedures detailed in this appendix are in accordance with ISO 14155. Both the investigator and Sponsor will comply with all local medical device reporting requirements. The detection and documentation procedures described in this protocol apply to all Sponsor medical devices provided for use in the study. See Section 6.1 for the list of Sponsor medical devices.

Definition of Adverse Event

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the medical device. This definition includes events related to the medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to devices.

An adverse device effect (ADE) is defined as an adverse event related to the use of a medical device. This definition includes any AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation; any malfunction of the medical device as well as any event resulting from use error or from intentional misuse of the medical device.

Events meeting the AE definition include:

- any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (for example, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgement of the investigator (that is, not related to progression of underlying disease)
- exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- new conditions detected or diagnosed after study intervention administration even though they may have been present before the start of the study
- signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction, and
- signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdose should be reported regardless of sequelae.

The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, “lack of efficacy” or “failure of expected pharmacological action” also constitutes an AE or SAE.

Events not meeting the AE definition include:

- any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition
- the disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition
- medical or surgical procedure (for example, endoscopy, appendectomy): the condition that leads to the procedure is the AE
- situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

All AEs shall be reported to the Sponsor as soon as possible upon site awareness via eCRF.

Definition of Serious Adverse Event

An SAE is defined as any adverse event that led to any of the following:

a. death,
b. serious deterioration in the health of the subject, that resulted in any of the following:
   vi. life-threatening illness or injury,
   vii. permanent impairment of a body structure or a body function,
   viii. hospitalisation or prolongation of patient hospitalisation,
   ix. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
   x. chronic disease,
c. foetal distress, foetal death, or a congenital physical or mental impairment or birth defect

Severe hypoglycaemic events must be reported to Lilly as an SAE.

All SAEs shall be reported to the Sponsor within 24 hours of site awareness via eCRF.

Definition of Serious Adverse Device Event

A Serious adverse device effect (SADE) is defined as an ADE that has resulted in any of the consequences characteristic of a SAE.

Definition of Unanticipated Adverse Device Event

A UADE is a SAE 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 clinical 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 (see Section 2.4).

Definition of Device Deficiency

A device deficiency is any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer.

When the ability to use the study intervention safely is impacted, the following are also DDs:

- Deficiencies in labelling information, and
- Use errors for device or drug-device combination products due to ergonomic design elements of the product.

Device deficiencies related to study interventions used in clinical trials are collected to ensure the safety of participants, monitor quality, and to facilitate process and product improvements. Investigators will instruct participants to contact the site as soon as possible if he or she has a DD or problem with the study intervention so that the situation can be assessed.

An event may meet the definition of both a DD and an AE/SAE. In such cases, it should be reported as both a DD and as an AE/SAE.

Recording and Follow-Up of Adverse Event, Serious Adverse Events, and Device Deficiencies

- When an AE/SAE/DD occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/DD information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE, SAE, and DD information is reported on the appropriate data source. Note: An event may meet the definition of both a DD and an AE/SAE. In such cases, it should be reported as both a DD and as an AE/SAE.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Sponsor or designee in lieu of completion of the eCRF page for AE/SAE and sponsor DD form.
- There may be instances when copies of medical records for certain cases are requested by Sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Sponsor of designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:
    - **Mild**: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

- **Moderate**: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- **Severe**: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilised for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgement to determine the relationship.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
The investigator will also consult the IFU and/or product information for marketed products, in his/her assessment.
For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to Sponsor or designee. However, it is very important that the investigator always assess causality for every event before the initial transmission of the SAE data to Sponsor or designee.
The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include:

- additional laboratory tests or investigations
- histopathological examinations, or
- consultation with other HCPs.

If a participant dies during participation in the study or during a recognised follow-up period, the investigator will provide Sponsor or designee with a copy of any post-mortem findings including histopathology.

Reporting of Serious Adverse Events

The primary mechanism for reporting an SAE will be the electronic data collection tool (eCRF):

- If the electronic system is unavailable, then the site will use the SAE paper form (see next section) to report the event within 24 hours.
- All SAEs shall be reported to the Sponsor within 24 hours of site awareness.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information to the Sponsor by telephone.
- Contacts for SAE reporting can be found in site training package.

SAE/Device Deficiency Regulatory Reporting

Prompt notification by the investigator to the Sponsor of a SAE/DD is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, EC, and investigators, according to Section 8 Reporting Timelines of MDCG 2020-10/1. The reporting form will contain the appropriate information called out in the Clinical Investigation Summary Safety Reporting Form per MDCG 2020-10/1 Appendix.
An investigator who receives an investigator safety report describing a SAE/DD or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the IFU and will notify the EC, if appropriate according to local requirements.

Appendix 3. Contraceptive and Barrier Guidance

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below). If fertility is unclear (for example, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

premenarchal
premenopausal female with 1 of the following:

- documented hysterectomy
- documented bilateral salpingectomy, and
- documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above (for example, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Determination can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Postmenopausal female, defined as, women with:

- 12 months of amenorrhea for women >55, with no need for FSH
- 12 months of amenorrhea for women >40 years old with FSH ≥40 mIU/mL and no other medical condition such as anorexia nervosa and not taking medications during the amenorrhea (e.g., oral contraceptives, hormones, gonadotropin releasing hormone, anti-oestrogens, selective estrogenic receptor modulators, or chemotherapy that induced amenorrhea)

Contraception Guidance

Women of childbearing potential must use either 1 highly effective method of contraception or a combination of 2 effective methods of contraception. The participant may choose to use a double- barrier method of contraception (see Table APP.10.1.)

Barrier protection methods without concomitant use of a spermicide are not an effective or acceptable method of contraception. It should be noted, however, that the use of male and female condoms as a double-barrier method is not considered acceptable due to the high failure rate when these barrier methods are combined.

Table APP.10.1. Methods of Contraception

Highly Effective Methods of Contraception	Effective Methods of Contraception (Must Use Combination of 2 Methods)
Combined oral contraceptive pill and mini pill	Male condom with spermicide
Vaginal ring (e.g., NuvaRing®)	Female condom with spermicide
Implantable contraceptives	Diaphragm with spermicide
Injectable contraceptives (e.g., Depo-Provera®)	Cervical sponge with spermicide
Intrauterine device (e.g., Mirena®)	Cervical cap with spermicide
Contraceptive patch (ONLY women <198 lb or 90 kg)	
Bilateral tubal occlusion	
Total abstinence	
Vasectomy	

Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

Collection of Pregnancy Information

Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

Appendix 4. Provisions for Changes in Study Conduct During Exceptional Circumstances

The Investigator/Site must consult the Sponsor or Sponsor representative before implementing any mitigation measures, such as those relating to COVID-19.

If any mitigation measure related to COVID-19 impacts on the study participants, for example shipping study supplies to the participant's home, conducting participant visits remotely, performing trial activities at a site/facility other than the trial site, the participants must consent to this change.

Verbal consent is required and should be documented in the participants medical records. Participant consent must be confirmed before implementing the mitigation measure.

Participant consent is not required to conduct remote monitoring activities.

Prospective protocol waivers remain unacceptable, and participants should not be included in trials without proper eligibility assessment, including performance of planned tests, and written informed consent according to national laws and regulations.

Study Consent

In cases where an update to the ICF, which requires study participants to be reconsented, occurs during the trial, the sites should provide the updated ICF to study participants by email, mail, or courier before verbal re-consent is obtained. Verbal consent should be documented by the site and confirmed by way of normal consent procedure at the earliest opportunity when the study participants are back at the site.

Remote consent can be leveraged in situations where verbal consent alone would not be deemed appropriate or sufficient to ensure that the participant was able to provide fully informed consent. Remote consent would be appropriate in situations where participants are required to consent to new enrolment (e.g., roll-over studies) or new participants are consenting to new studies. The Sponsor or Sponsor representative should be consulted on the specific process steps for this scenario.

Participant Visits

In case of severe external disruptions, participants may not be able to come back to the site for their scheduled visits due to traffic restrictions and safety concerns. In these instances, remote visits may be conducted to ensure participants' safety, study quality, and integrity. The same principles and steps should be followed as for any routine situation when a participant cannot come to the site for a planned visit and the duration of the restriction is not known.

Direct entry into eCRF is not allowed. Source records should still be created by the site or mobile health care provider per site-specific strategy and as indicated on the site delegation of authority.

The Sponsor or Sponsor representative **must** be consulted on the specific process steps before implementing the mitigation measure.

The following types of alternative participant visits can be considered:

1. **Remote Visit** is defined as a phone call or videoconference (virtual) visit used to replace a protocol required on-site visit where remote data can be collected. A new visit in the CRF is triggered to collect data. These visits should be considered when:
    a. In-person site visits are not possible because the site is not conducting research visits, or the participant is not able or unwilling to travel to the site.
    b. Collection of limited data over the phone or videoconference will help ensure that safety risks are mitigated.
    a. Per protocol physical visits are reduced or postponed, and it is important that the investigator continue collecting AEs from the participant through alternative means (e.g., by phone or videoconference).
2. **Mobile Visit** is defined as an in-home visit used to replace a protocol required on-site visit where necessary activities are performed by a contracted health care provide (e.g., nurse) or a member of the site staff (e.g., nurse study coordinator). Source data are collected, and those data needed within the CRF are sent/taken back to the site as source for data entry. These visits should be considered when:
    a. It is necessary to have participant contact for protocol required activities (e.g., physical examination, administration of participant reported outcome assessment).
    b. A health care provider is needed to administer medication.
    c. A health care provider is needed to collect specimens (e.g., blood specimen for central laboratory assessment).
3. **Alternate Site Visit** is defined as a visit conducted in-person at an alternative site participating in the same trial. These visits should be considered when:
    a. In-person site visit is needed; however, the participant's primary site is not available or is less convenient for the participant.

Additional Considerations:

- If videoconferencing is employed, international privacy requirements (e.g., HIPAA) must be considered. Consult with the Sponsor or Sponsor representative for appropriate technology solution enablement.
- Consent is required for visits in a participant's home.

Clinical Trial Supplies

Under certain circumstances a situation may occur where participants may not be able to return to site for scheduled visits due to numerous factors such as site restriction and/or safety concern and as such cannot receive their required study materials.

The following potential supply options may be considered when there are no alternate measures to meet participant needs:

1. Participants going to another investigator site for a visit
2. Designee obtaining CT materials on participant's behalf
    a. Must have participant's consent/authorisation and site must document

3. Investigator site staff delivering CT material to participant outside of clinic
    a. Site must document in participant files
4. Investigator site to participant shipment
    a. The investigator site should contact the participants prior to product shipment and inform them of the requirement to share his/her identity with a vendor. The site should document the non-opposition of the participant.
    b. The shipment of the drugs must be in accordance with the defined temperature and environmental conditions.
    c. The site must have a process or procedure to allow them to ship drug directly to a participant. The process/procedure should ensure material can be transported per label conditions; method of packing takes steps to ensure product protection.
    d. Shipment is made via an expedited method (i.e., overnight).
    e. There is confirmation the participant received material, and participant is instructed to not administer the product and contact the site for instructions if material is delivered damaged.
    f. The investigator site must ensure the traceability of the CT material throughout the process.

Lilly will reimburse sites for the additional expense related to the cost of using couriers for CT delivery, in accordance with national legislation and/or guidance.

Remote Study Monitoring

Remote monitoring activities may be implemented as a mitigation by the Sponsor or Sponsor representative to maintain oversight of study activities while on-site monitoring visits, including Site Initiation Monitoring Visits and Close Out Visits, cannot be completed.

Provision of copies of medical records, even pseudonymised, for the purpose of remote monitoring is not allowed.

Appendix 5. Abbreviations

Term	Definition
AACE	American Association of Clinical Endocrinology
ADA	American Diabetes Association
ADE	adverse device effect
AE	Adverse event
App	application
ATTD	Advanced Technologies and Treatments for Diabetes
AWS	Amazon Web Services
BG	blood glucose
BLE	Bluetooth® Low Energy
CE	Conformité Européenne
CFR	Code of Federal Regulations
CGM	continuous glucose monitor/monitoring
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CSR	clinical study report
CT	computed tomography
DD	device deficiency
DKA	diabetic ketoacidosis
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EU	European Union
FOIA	Freedom of Information Act
FPV	First participant visit
GDPR	General Data Protection Regulation
HbA1c	Glycated haemoglobin
HCP	healthcare professional
HFS-SF	Hypoglycaemia Fear Survey – Short Form
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
EC	Ethics Committee

Term	Definition
IFU	Instructions for Use
ISO	International Organisation for Standardisation
Lilly	Eli Lilly and Company
LPV	Last participant visit
MBD	missed bolus dose
MDD	Medical Device Directive
MDR	Medical Device Regulation
MDSW	medical device software
MRI	Magnetic Resonance Imaging
PHI	Protected Health Information
PoC	Point-of-care
PwD	Person/People with diabetes
RMA	research mobile app/application
SADE	Serious adverse device effect
SAE	serious adverse event
SD	Standard Deviation
SMBG	self-monitoring of blood glucose
SoA	schedule of activities
T1D	type 1 diabetes
T2D	type 2 diabetes
TAR	Time above range
TBR	Time below range
TIR	Time-in-range
UADE	unanticipated adverse device effect
US(A)	United States (of America)
WOCBP	Women of childbearing potential

Appendix 6. Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment Version 7: (06 September 2023)

DOCUMENT HISTORY	
Document	**Date**
Version 7.0	06 September 2023
Version 6.0	29 June 2023
Version 5.0	17 May 2023
Version 4.0	10 May 2023
Version 3.0	28 April 2023
Version 2.0	14 April 2023
Original Protocol	23 January 2023

Overall Rationale for the Amendment

This protocol has been amended to incorporate feedback from Le Comité de Protection des Personnes (CPP).

11. References

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11.2. Previous Investigations of the Humalog Tempo pen and Tempo Smart Button

Products used in this study are CE-marked/EMA-approved. Information on prior product testing and/or clinical investigations is available in the

- Humalog Tempo Pen Package Insert, and
- Tempo Smart Button IFU.

Additionally, Study F3Z-MC-IOQY (Taylor et al. 2021) has been conducted with Humalog Tempo Pen and Tempo Smart Button in participants with T1D and T2D. One of the secondary objectives of this study was to assess the overall ease of use of the Tempo Pen/Smart Button as part of an integrated insulin management system.

The Smart Button, as part of the integrated insulin management system, was reported as easy to use. Additionally, the majority of participants (78.1%) responded that they would be highly likely or somewhat likely to include the system in their diabetes management. Likewise, the majority of site personnel (64.3%) responded that they were highly likely or somewhat likely to recommend the system to their patients.

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