Insulet Corporation

Statistical Analysis Plan

for

RAndomized Controlled Trial to Demonstrate the Efficacy of the Omnipod® 5 with FreeStyle Libre 2 Compared to Multiple Daily Injections for TreAtmeNT of Type 1 Diabetes (Omnipod 5 RADIANT Study)

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Document Approval

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1 PURPOSE

The purpose of this Statistical Analysis Plan (SAP) is to describe the statistical methodology that is used to confirm the safety and effectiveness of the "RAndomized Controlled Trial to Demonstrate the Efficacy of the Omnipod® 5 with FreeStyle Libre 2 Compared to Multiple Daily Injections for TreAtmeNT of Type 1 Diabetes" (RADIANT) study. Should there be a discrepancy between the study protocol and this SAP, the content of the SAP shall prevail.

2 STUDY DESIGN

2.1 STUDY DESIGN OVERVIEW

This is a prospective, randomized, parallel-group multicenter trial, followed by an extension period during which both groups use the Omnipod 5 System.

A total of up to 250 pediatric and adult participants will be screened for this study. Up to 200 participants across up to 20 investigational sites in France, Belgium, and the United Kingdom, comprised of 120 children (aged 4-17.9 years old) and 80 adults (aged 18-70 years old) with type 1 diabetes currently on multiple daily injections (MDI) and sensor therapy with an HbA1c between 7.5-11% (58-97 mmol/mol), inclusive, will be enrolled.

Subjects will be randomized in a 2:1 allocation to Intervention Arm (Omnipod 5 System with FreeStyle Libre 2 sensor) or Control Arm (MDI with FreeStyle Libre 2 sensor).

Following a two-week standard therapy period where sensor data will be collected, participants will be randomized (2:1 ratio [Intervention:Control]) to either:

- Intervention group: Omnipod 5 System with FreeStyle Libre 2 Sensor or
- Control group: MDI with FreeStyle Libre 2 Sensor

Period 1:

Both groups will participate for a total of 26 weeks after completion of standard therapy. During the first 13-week randomized period, participants in the Control group will continue using MDI therapy with their glucose sensor. Participants in the Intervention group will onboard onto the Omnipod 5 System. At the conclusion of the 13-week randomized period, the Control group will onboard and use the Omnipod 5 System for an additional 13 weeks. Both groups will continue using the Omnipod 5 System for the remainder of the 26 weeks.

Period 2:

Following Period 1, participants in France and Belgium will be offered the option to continue use of the Omnipod 5 System through commercialization.

All participants will use the FreeStyle Libre 2 Sensor for the duration of the study.

2.2 INVESTIGATIONAL DEVICE

The devices used in the Intervention group include:

- Omnipod 5 System, comprised of the following components:
  - Omnipod 5 Pod
  - Omnipod 5 App (on the Insulet-provided Controller)
- Abbott FreeStyle Libre 2 Glucose Sensor ("FreeStyle Libre 2")

The devices used in the Control group include:

- Participant's own MDI supplies
- Abbott FreeStyle Libre 2 Glucose Sensor

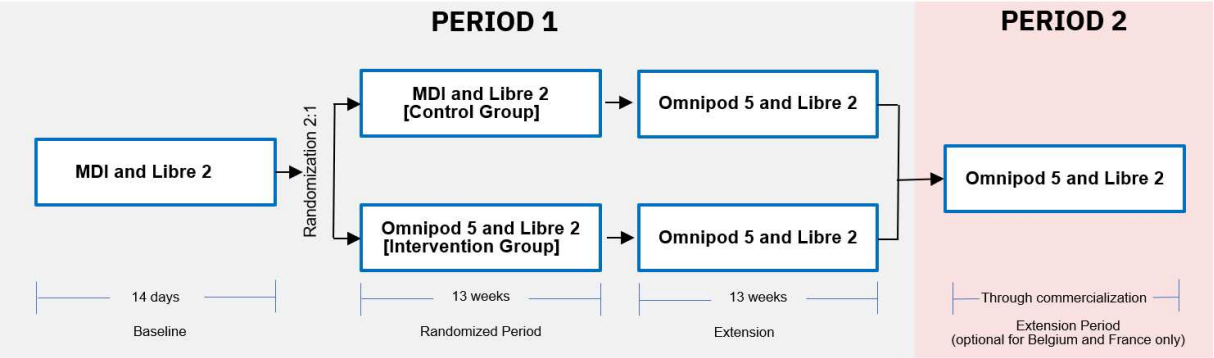
2.3 STUDY SCHEDULE

The study is expected to be completed in approximately 32 months, which includes clinical site initiation to completion of all data entry, monitoring procedures, and report finalization. Each participant is expected to participate for approximately 6 months (Period 1). Participants that agree to take part in Period 2 (France and Belgium only) may participate until the Omnipod 5 System is commercially available (approximately an additional 6-12 months).

Briefly, the study will consist of:

1. A Baseline 14-day standard therapy period (Period 1)
2. A 13-week randomized period (Period 1), followed by
3. 13-week extension period with both groups using the Omnipod 5 System (Period 1).
4. An optional extension period with both groups using the Omnipod 5 System until the Omnipod 5 System is commercially available(Period 2, for France and Belgium only).

Figure 1. Study Schematic



2.4 STUDY SUCCESS

The study will be deemed successful if the primary endpoint is met.

2.5 RANDOMIZATION

This is a prospective, randomized, parallel-group multicenter trial followed by an extension period during which both groups use the Omnipod 5 System.

After completing the 14-day standard therapy period, all participants will transition to the 13-week randomized period. At the conclusion of the standard therapy period, participants who meet all eligibility criteria, have completed all screening assessments, and have met the sensor device usage and data criteria will be randomized 2:1 (Intervention:Control) using a computer-generated randomization scheme stratified by site and by age group (<18 years, ≥18 years). A permuted-block randomization scheme will be implemented to balance group assignments. Randomization will be assigned via study database access during Visit 3 to one of the two study groups: Intervention group (Omnipod 5 System with FreeStyle Libre 2 Sensor) or Control group (Multiple daily injections therapy with FreeStyle Libre 2 Sensor)).

Participants randomized to the Intervention group will onboard onto the Omnipod 5 System during Visit 4. Participants randomized to the Control group will continue their usual MDI and sensor therapy during the 13 weeks.

2.6 POINT OF ENROLLMENT

A subject is considered enrolled into the study when the participant commences the 14-day standard therapy period (at Visit 2) or when the participant shares their sensor data for an abbreviated standard therapy period. Participants who do not meet the eligibility criteria will not continue in the study and will be considered screen failures.

2.7 SAMPLE SIZE

The study is powered at 90% to detect a between-group difference of 0.5% in change from baseline in HbA1c at 13 weeks and assuming a standard deviation of 0.7% in each group for children (aged 4-17.9 years old) or 0.5% for adults (aged 18-70 years old). Under these assumptions and with 2:1 (Intervention:Control) randomization, a total sample size of 96 children (64 Intervention, 32 Control) and 51 adults (34 Intervention, 17 Control) is required. To allow for attrition of up to 20% for children and 35% for adults, a total sample size of up to 200 will be enrolled (120 children, 80 adults) to obtain a minimum of 147 (96 children and 51 adults) completing the primary 13-week randomization period. A maximum of 250 participants will be screened.

The anticipated difference and standard deviations were projected from the Omnipod 5 Pivotal study (NCT04196140). PASS 2022 was used for sample size calculations.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 PRIMARY OBJECTIVE AND ENDPOINT

The primary objective is to demonstrate superior efficacy of the Omnipod 5 System compared to MDI and sensor therapy in children and adults with type 1 diabetes. The primary endpoint is defined as follows.

- Per-participant change from baseline in HbA1c at 13 weeks of randomized period between Intervention and Control group.

3.2 SECONDARY OBJECTIVES AND ENDPOINTS

The secondary objective is to demonstrate additional measures of efficacy and safety of the Omnipod 5 System compared to MDI and sensor therapy in children and adults with type 1 diabetes.

The following secondary per-participant endpoints will be evaluated and compared in the Intervention group vs. Control group at the end of 13-week randomized period. Unless otherwise indicated, these endpoints will be analyzed for the total cohort. The secondary endpoints will be tested hierarchically for statistical significance in the following order:

1. Percentage of time in range 70-180 mg/dL (3.9-10.0 mmol/L)
2. Percentage of time <54 mg/dL (3.0 mmol/L) (non-inferior)
3. Percentage of time >180 mg/dL (10.0 mmol/L)
4. Percentage of time >300 mg/dL (16.7 mmol/L)
5. Percentage of time <70 mg/dL (3.9 mmol/L) (non-inferior)
6. Change from baseline in HbA1c for participants ≥18 years of age at baseline
7. Change from baseline in HbA1c for participants <18 years of age at baseline
8. Percentage of time in range 70-180 mg/dL (3.9-10.0 mmol/L) for participants ≥18 years of age at baseline
9. Percentage of time in range 70-180 mg/dL (3.9-10.0 mmol/L) for participants <18 years of age at baseline
10. Change from baseline in HbA1c in participants with baseline HbA1c ≥8% (64 mmol/mol)
11. Change from baseline in PSQI total score
12. Change from baseline in T1-DDS total score for participants ≥18 years of age at baseline
13. Change from baseline in HCS total score for participants ≥18 years of age at baseline
14. Percentage of time <70 mg/dL (3.9 mmol/L)
15. Percentage of participants achieving HbA1c <7% (53 mmol/mol)
16. Change from baseline in EQ-5D-3L index score
17. Change from baseline in total daily insulin (TDI) (units/kg) for participants ≥18 years of age at baseline
18. Percentage of time <54 mg/dL (3.0 mmol/L)

3.3 EXPLORATORY ENDPOINTS

Period 1 – 13-week Randomized Period

The following exploratory endpoints will be evaluated and compared in the Intervention group vs. Control group at the end of the 13-week randomized period. Unless otherwise indicated, these endpoints will be analyzed for the total cohort, for participants < 18 years of age, and for participants ≥18 years of age (as applicable):

CGM-Derived Outcomes

- Percentage of time <54 mg/dL (3.0 mmol/L)
- Percentage of time <70 mg/dL (3.9 mmol/L)
- Percentage of time >180 mg/dL (10.0 mmol/L)
- Percentage of time >300 mg/dL (16.7 mmol/L)
- Percentage of time >250 mg/dL (13.9 mmol/L)
- Mean glucose (mg/dL and mmol/L)
- Coefficient of variation (%)

Glycemic Targets

- Percentage of participants achieving HbA1c <7% (53 mmol/mol)
- Percentage of participants achieving <6.5% (48 mmol/mol)
- Percentage of participants in range 70-180 mg/dL (3.9-10.0 mmol/L) >70% of time
- Percentage of participants in range 70-180 mg/dL (3.9-10.0 mmol/L) >70% of time and below range <70 mg/dL (3.9 mmol/L) (TBR) <4% of time

Insulin and Weight Change

- Change from baseline in total daily insulin (TDI) (units/kg) for participants <18 years of age at baseline
- Change from baseline in total daily insulin (TDI) (units)
- Change from baseline in Body Mass Index (BMI) (kg/m^2) or BMI z-score as appropriate.
- Change from baseline in weight (kg)

Safety

- Number of hypoglycemic events as measured by the glucose sensor (<70 mg/dL for ≥15 minutes; <54 mg/dL for ≥15 minutes)
- Number of hyperglycemia events as measured by the glucose sensor (≥300 mg/dL for ≥1 hour)
- Number of episodes of severe hypoglycemia
- Number of episodes of DKA

Patient Reported Outcomes (PROs)

- T1 Diabetes Distress Scale (T1-DDS)
- Hypoglycemic Confidence Scale (HCS)
- Pittsburgh Sleep Quality Index (PSQI)
- EQ-5D-3L, EQ-5D-3L proxy version 1

- Diabetes Quality of Life Brief (DQOLBrief)
- System Usability Scale (SUS)
- Insulin Dosing Systems: Perceptions, Ideas, Reflections, and Expectations (INSPIRE)
- Patient Health Questionnaire-2 (PHQ-2)
- Clarke Hypoglycemia Awareness
- System opinion questions
- Time away from school/work
- Proportion of participants achieving a Total Score > 5 (Poor Sleepers) on the PSQI questionnaire at 13 weeks[1].
- Proportion of participants achieving a minimally clinically important difference (MCID) of ≥0.19 points (improvement) on the T1-DDS questionnaire total score at 13 weeks[2].
- Proportion of participants achieving MCID score of ≥3 on the HCS questionnaire at 13 weeks[3] for participants ≥18 years of age at baseline
- Proportion of participants achieving a Minimally Detectable Difference (MDC) improvement of Change from Baseline > 0.5*Standard Deviation (SD) on the EQ-5D-3L questionnaire index score at 13 weeks [4].

Device Use

- Percentage of time spent in Automated Mode and in Manual Mode
- Number of boluses delivered per day
- Cumulative number of person-days spent at each available glucose target setting

The following outcomes will be assessed separately during the day (06:00–23:59 hours) and during the night (00:00–05:59) compared in the Intervention group vs. Control group at the end of 13-week randomized period.

- Percentage of time in range 70-180 mg/dL (3.9-10.0 mmol/L)
- Percentage of time <54 mg/dL (3.0 mmol/L)
- Percentage of time <70 mg/dL (3.9 mmol/L)
- Percentage of time >180mg/dL (10.0 mmol/L)
- Percentage of time >300 mg/dL (16.7 mmol/L)

[1] Buysse, Daniel J, Charles F. Reynolds, Timothy H. Monk, Susan R. Berman and David J. Kupfer. The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. Psychiatry Research 28 (1989): 193-213.
[2] Fisher L, Hessler D, Polonsky W, Strycker L, Masharani U, Peters A. Diabetes distress in adults with type 1 diabetes: Prevalence, incidence and change over time. J Diabetes Complications. 2016 Aug;30(6):1123-8. doi: 10.1016/j.jdiacomp.2016.03.032. Epub 2016 Apr 4. PMID: 27118163; PMCID: PMC4949147.
[3] Polonsky WH, Fisher L, Hessler D, Edelman SV. Investigating Hypoglycemic Confidence in Type 1 and Type 2 Diabetes. Diabetes technology & therapeutics. 2017;19(2):131-6.
[4] Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care 2003;41:582e92.

- Percentage of time >250 mg/dL (13.9 mmol/L)

Period 1 – 13-week Extension Period

The following exploratory endpoints will be evaluated at the end of the Omnipod 5 System use and compared to the start of the Omnipod 5 System use (either at the end of 26 weeks for the Intervention group as compared to baseline, or at the end of 26 weeks compared to the end of 13-week randomized period for the Control group). These endpoints will be analyzed for the total cohort, for participants <18 years of age, and for participants ≥18 years of age.

Glycemic Outcomes
- HbA1c at 13 weeks extension of Period 1

CGM-Derived Outcomes
- Percentage of time in range 70–180 mg/dL (3.9-10.0 mmol/L)
- Percentage of time <54 mg/dL (3.0 mmol/L)
- Percentage of time <70 mg/dL (3.9 mmol/L)
- Percentage of time >180mg/dL (10.0 mmol/L)
- Percentage of time >300 mg/dL (16.7 mmol/L)
- Percentage of time >250 mg/dL (13.9 mmol/L)

Glycemic Targets
- Percentage of participants achieving HbA1c <7% (53 mmol/mol)

Patient Reported Outcomes (PROs)
- T1 Diabetes Distress Scale (T1-DDS)
- Hypoglycemic Confidence Scale (HCS)
- Pittsburgh Sleep Quality Index (PSQI)
- EQ-5D-3L, EQ-5D-3L proxy version 1
- Diabetes Quality of Life Brief (DQOLBrief)
- System Usability Scale (SUS)
- Insulin Dosing Systems: Perceptions, Ideas, Reflections, and Expectations (INSPIRE)
- Patient Health Questionnaire-2 (PHQ-2)
- Clarke Hypoglycemia Awareness
- System opinion questions
- Time away from school/work

Device Use
- Percentage of time spent in Automated Mode and in Manual Mode
- Number of boluses delivered per day
- Cumulative number of person-days spent at each available glucose target setting

Period 2 Extension

The following exploratory endpoints will be evaluated for the participants in France and Belgium only at the end of the Omnipod 5 System use and compared to the start of the Omnipod 5 System use (either at the end of the extension for the Intervention group as compared to baseline, or at the end of the extension compared to the end of 13-week randomized period for the Control group). These endpoints will be analyzed for the total cohort, for participants <18 years of age, and for participants ≥18 years of age.

Glycemic Outcomes
- HbA1c at 3, 6, and 9 months of Period 2
- Change from baseline in HbA1c at 3, 6, and 9 months of Period 2

CGM-Derived Outcomes
- Percentage of time <54 mg/dL (3.0 mmol/L)
- Percentage of time <70 mg/dL (3.9 mmol/L)
- Percentage of time >180mg/dL (10.0 mmol/L)
- Percentage of time in range 70–180 mg/dL (3.9-10.0 mmol/L)
- Mean Glucose

Glycemic Targets
- Percentage of patients having time in range 70-180 mg/dL (3.9-10.0mmol/L) >70% of time
- Percentage of patients having time below range <70 mg/dL (3.9 mmol/L) <4% of time

Insulin and Weight Change
- Insulin usage (units, units/kg)
- Change from baseline in BMI, or BMI z-score as appropriate, at the end of Period 2

Safety
- Incidence rate of severe hypoglycemia
- Incidence rate of diabetic ketoacidosis (DKA)

Patient Reported Outcomes (PROs)
- T1 Diabetes Distress Scale (T1-DDS)
- Hypoglycemic Confidence Scale (HCS)
- Diabetes Quality of Life Brief (DQOLBrief)

Device Use
- Percentage of time spent in Automated Mode

4 ANALYSIS OF PRIMARY ENDPOINT

4.1 PRIMARY ANALYSIS

The primary endpoint will be tested for statistical significance in the modified intention to treat (mITT) analysis set (defined in Section 7.2.2) at a two-sided significance level of 5%. Hypothesis testing for the secondary endpoints will commence if and only if the primary endpoint is found to be statistically significant (two-sided p-value ≤0.05). Strict

control of Type I error will be maintained with a hierarchical testing procedure, with secondary endpoints tested in the order listed above.

Each secondary endpoint with a two-sided p-value ≤0.05 (or one-sided p-value of ≤0.025, as appropriate) is considered to be met until a secondary endpoint with a two-sided p-value >0.05 (or one-sided p-value of >0.025, as appropriate) is encountered. That secondary endpoint, and all subsequent secondary endpoints, are considered to not be met irrespective of their observed p-values.

Hypothesis testing for the exploratory endpoints may be performed based on the clinical interest or relevance of the outcome for future study hypothesis generation. Methods for exploratory endpoints analysis are described in Section 5.2.1.

The primary and secondary endpoints will be summarized for the mITT and per protocol (PP) analysis sets (defined in Section 7.2). If the PP analysis set does not differ from the mITT analysis set, separate analyses will not be presented.

4.1.1 Change from Baseline in HbA1c

The primary endpoint is the change from baseline in HbA1c at 13 weeks between the Intervention and Control groups. The null hypothesis states that the mean change from baseline in HbA1c at 13 weeks in the Intervention group is equal to the mean change from baseline in HbA1c at 13 weeks in the Control group. The alternative hypothesis states that the mean change from baseline in HbA1c at 13 weeks in the Intervention group is not equal to the mean change from baseline in HbA1c at 13 weeks in the Control group.

Formally, the hypotheses associated with primary endpoint are:

- H_0: $\mu_I - \mu_C = 0$
- H_A: $\mu_I - \mu_C \neq 0$
  where μ_I and μ_C are the population means of change from baseline in HbA1c at 13 weeks in the Intervention and Control groups, respectively.

The calculation of change from baseline in HbA1c is described in Section 7.4.1 of this document.

The primary endpoint will be analyzed with a linear mixed effects model (LMM) with change from baseline in HbA1c at 13 weeks as the outcome, and randomized treatment group as a fixed effect. The following variables will be included in the model as fixed effects: age, sex, duration of diagnosis, and baseline HbA1c value. Country and/or site may be included in the model as random effects, depending on the results of the poolability assessment described in Section 4.3 of this document. The assessment of significance will be based on the least squares means estimate of the difference between treatment groups produced by the model.

Standard residual diagnostics will be performed for all analyses associated with the primary endpoint. It is expected that the primary outcome will follow an approximately normal distribution, however, residual values will be examined to confirm an approximate normal distribution. If values are highly skewed, then robust regression using M-estimation will be used instead. In this case, the model will include HbA1c at 13 weeks as the dependent variable, baseline HbA1c, age, sex, and duration of diagnosis as the covariates, and missing data will be handled using multiple imputation as described in Section 7.6.

The primary analysis will utilize the mITT analysis set and will be tested at a two-sided significance level of 5%. If there is evidence of heterogeneity either across countries or study sites based on the poolability analysis, a random effect for country or site, as appropriate, will also be included. The study will be assumed to be successful if the primary endpoint is considered to be met; that is, the treatment group fixed effect in the LMM is significant at a two-sided significance level of 5%.

4.1.2 Handling of Missing Data

Handling of missing data for the primary endpoint is described in Section 7.6 of this document.

4.2 SENSITIVITY ANALYSIS

The following sensitivity analysis will be performed for the primary endpoint.

4.2.1 Complete Cases Only

The primary analysis will be replicated including only participants with non-missing HbA1c at baseline and follow-up. This assumes missing completely at random (MCAR).

4.2.2 Worst-Case and Tipping Point Analysis

The Worst-Case Scenario sensitivity analysis will be applied to subjects with missing values for change from baseline in HbA1c at 13 weeks, assuming the following:

- Subjects randomized to Omnipod 5 arm: Missing values at baseline will be imputed with the lowest observed non-missing baseline HbA1c value for the Omnipod 5 group, and missing values at 13 weeks will be imputed with the highest observed non-missing HbA1c value for the Omnipod 5 group at 13 weeks. This will result in the worst possible outcome (i.e., smallest change in HbA1c) for the subjects randomized to the Omnipod 5 arm.
- Subjects randomized to Control arm: Missing values at baseline will be imputed with the highest observed non-missing baseline HbA1c value for the Control group, and missing values at 13 weeks will be imputed with the lowest observed on-missing HbA1c value for the Control group at 13 weeks. This will result in the best possible outcome (i.e., greatest change in HbA1c) for the subjects randomized to the Control arm.

If the results of the worst-case analysis greatly differ from the primary analysis of the endpoint, a two-way tipping point sensitivity analysis will be performed to evaluate the possibility of missing not at random (MNAR).

First, multiple imputation will be applied to missing HbA1c assuming MAR, as described above. This procedure will then be repeated applying various shifts to the imputed values. Since the reasons for missing data may vary by treatment group, a separate shift will be applied for each treatment group. A shift of zero for both treatment groups is equivalent to the model assuming MAR. A positive shift indicates that we expect HbA1c to be worse in that treatment group for those with missing values than those with observed data. The range of shifts that are considered will include scenarios where the outcomes for patients missing data are worse among patients randomized to the treatment arm than those randomized to the control arm. The goal is to examine how far one needs to shift for the results of the study to tip from significant to not significant for between-treatment comparison. Tipping points that change the significance will be reported and clinically evaluated for whether such points are considered plausible.

4.2.3 Covariate Adjustment

The primary analysis includes a pre-specified list of covariates. As an additional sensitivity analysis, any baseline demographic or clinical characteristics observed to be imbalanced between treatment groups will be added as covariates to the model for the primary endpoint. The determination of a meaningful baseline imbalance will be based on clinical judgement and not a p-value.

4.3 POOLABILITY

As the study plans to enroll sites in multiple countries (France, Belgium and the United Kingdom), the poolability will be assessed first by country, and then by site.

4.3.1 Poolability by Country

A linear model with treatment group and country as fixed effects for change in HbA1c at 13 weeks from baseline will be fit for the comparison of treatment groups. The model will also include treatment group by country interaction term. A p-value for the interaction term of <0.15 will be considered to indicate heterogeneity, and a random effect for country will be included in the primary analysis model as described in Section 4.1 of this document. If the p-value for the interaction term is ≥0.15, random effect for country will not be included in any analyses.

4.3.2 Poolability by Site

If the p-value for the interaction term from the poolability by country assessment is ≥0.15, a linear model with treatment group and site as fixed effects for change in HbA1C at 13 weeks from baseline will be fit for the comparison of treatment groups. The model will also include treatment group by site interaction term. A p-value for the interaction term of <0.15 will be considered to indicate heterogeneity, and a random effect for site will be included in the primary analysis model as described in Section 4.1 of this document. If

the p-value for the interaction term is ≥0.15, random effect for site will not be included in any analyses.

If the p-value for the interaction term from the poolability by country assessment is <0.15, a linear model with treatment and study site as fixed effects for change in HbA1c at 13 weeks from baseline, and a treatment by site interaction, will be fit for each country separately. A p-value for the interaction term of <0.15 will be considered to indicate heterogeneity within that country. If the p-value for the interaction term from any of the country-specific models is <0.15, both country and site will be included as random effects in the primary analysis. If the p-value for all of the interaction terms for the country-specific models is ≥0.15, random effect only for country will be included in the primary analysis.

For the poolability analysis that assesses homogeneity within each country, sites with ≤5 subjects contributing to analysis will be combined into pseudo-centers of at least 10 subjects, or combined with existing centers to make sure that each site contributes at least 10 subjects. If possible, such grouping will be done within country. If site is included in other analyses, e.g., random effect in the analysis of primary endpoint, the same approach of combining sites will be used.

4.4 SUBGROUP AND STRATIFIED ANALYSES

Regardless of results of poolability analysis of primary endpoint, the primary endpoint will be further explored to understand the treatment effect. The general approach for these exploratory analyses will be to add an interaction term for the subgroup factor by treatment to the primary and secondary endpoint models described above. Factors expected to include are: country, sex, age, BMI, and baseline HbA1c.

Primary and secondary endpoints will be summarized with descriptive statistics at baseline, end of 13-week randomized period, and change from baseline at the end of the 13-week randomized period for the Intervention and Control groups, stratified by the following groups.

- Country (United Kingdom, France, and Belgium)
- Demographic measures (e.g., sex, age breakdowns)
- BMI (≤25 vs >25 kg/m^2)
- Baseline TIR (≥70%, 60 to <70%, and <60%)
- Baseline HbA1c (<8%, 8 to <9%, and ≥9%)

Additional stratification analysis will be included for the outcomes as described in Section 3, which will comprise:

- Day and night (daytime: 6AM to <12AM; nighttime as 12AM to <6AM)
- Age group (adults and children)

5 ANALYSIS OF OTHER ENDPOINTS

5.1 ANALYSIS OF SECONDARY ENDPOINTS

If the primary endpoint is found to be statistically significant at a two-sided significance level of 5%, testing for the secondary endpoints can commence. Secondary endpoints will be tested in a hierarchical fashion at a two-sided significance level of 5% (or one-sided significance level of 2.5% as appropriate). Strict type I error control will be maintained with the hierarchical testing procedure. Each endpoint with a two-sided p-value ≤0.05 (or one-sided p-value of ≤0.025, as appropriate) is considered to be met until a secondary endpoint with a two-sided p-value >0.05 (or one-sided p-value of >0.025, as appropriate) is encountered. That secondary endpoint, and all subsequent secondary endpoints, are considered to not be met irrespective of their observed p-values.

The primary analysis for all secondary endpoints will utilize the mITT analysis set and will be tested at a two-sided significance level of 5% or a one-sided significance level of 2.5%, as appropriate. If there is evidence of heterogeneity either across countries or study sites based on the poolability analysis, a random effect for country and/or site, as appropriate, will also be included.

5.1.1 Analysis of Change from Baseline Endpoints

The change from baseline secondary endpoints will be analyzed using a LMM effects model with each of the secondary endpoints as the outcome, and randomized treatment group as a fixed effect. This is similar to the method used for the analysis of primary endpoint. The following variables will be included in the model: age, sex, duration of diagnosis, and baseline value of the outcome being tested. The factors included in the model may differ between endpoints. The assessment of significance for each change from baseline endpoint will be based on the least squares means estimate of the difference between treatment groups produced by the model.

Standard residual diagnostics will be performed for all secondary endpoint analyses. Residual values will be examined to confirm an approximate normal distribution. If values are highly skewed, then robust regression using M-estimation will be used instead. In this case, the model will include the outcome value at 13 weeks as the dependent variable, age, sex, duration of diagnosis, and the baseline value of the outcome being tested as the covariates, and missing data will be handled using multiple imputation as in Section 7.6.

5.1.2 Analysis of CGM-Derived Endpoints

The CGM-derived secondary endpoints will be analyzed using a repeated measures linear mixed effects model (RLMM) with time in the specified range as the dependent variable. The correlation between baseline and follow-up will be modelled using an unstructured covariance matrix. The model will include randomized treatment group, age, sex, and duration of diagnosis as fixed effects and may include site and/or country as random effects (based on the assessment of poolability for the primary endpoint). Visit will be included as the repeated effects term for time and an interaction term of visit and

treatment group will be included in the model. By including both baseline and 13 weeks in the predictor vector, the model allows participants to be included even if they do not have CGM-derived data at one of the two timepoints. The assessment of significance for each CGM-derived endpoint will be based on the least squares means estimate of the difference between treatment groups at 13 weeks produced by the model.

Missing data will be handled by using a direct likelihood approach which will allow participants to be included even if they only have data at one of the time points. The direct likelihood method approach assumes data are missing at random (MAR).

Standard residual diagnostics will be performed for all analyses associated with the secondary endpoints. It is expected that the primary outcome will follow an approximately normal distribution, however, residual values will be examined to confirm an approximate normal distribution. If values are highly skewed, then robust regression using M-estimation will be used instead. In this case, the model will include time in the specified range during the 13 weeks randomized period as the dependent variable, baseline time in the specified range as a covariate, and missing data will be handled using multiple imputation.

5.1.3 Binary Secondary Endpoints

Binary endpoints will be presented as the number and percent of participants achieving the endpoint with corresponding 95% asymptotic confidence limits in each group. Binary endpoints will be analyzed using a logistic mixed effects model using logit link function, with the endpoint as the outcome. The following variables will also be included in the model as fixed effects: randomized treatment group, age, sex, duration of diagnosis, and baseline continuous value of the outcome being tested (if available). A 95% confidence interval for the treatment group adjusted risk difference will be produced using parametric bootstrapping. The assessment of significance for each binary endpoint will be based on the least squares means estimate of the difference between treatment groups at 13 weeks produced by the model.

The missing data for the secondary endpoints will be handled according to Section 7.6

5.1.4 Hierarchy of Secondary Endpoints

The secondary endpoints will be testing in the following order:

5.1.4.1 Percentage of Time in Range (TIR) 70-180 mg/dL

The hypotheses associated with this endpoint are:

- H_0: $\mu_I - \mu_C = 0$
- H_A: $\mu_I - \mu_C \neq 0$

  where μ_I and μ_C are the population means of per-participant means of percentage of time in range (TIR) 70-180 mg/dL during the 13 weeks in the Intervention and Control groups, respectively.

The calculation of percentage of time in a specified range is described in Section 7.4.2 this document. This endpoint will be considered met if the least squares means estimate of the difference between treatment groups at 13 weeks in the RLMM is significant at a two-sided significance level of 5%.

5.1.4.2 Percentage of Time <54 mg/dL (Non-Inferiority)

The hypotheses associated with this endpoint are:

- H_0: $\mu_I - \mu_C \geq 1\%$
- H_A: $\mu_I - \mu_C < 1\%$
  where μ_I and μ_C are the population means of per-participant percentage of time <54 mg/dL during the 13 weeks in the Intervention and Control groups, respectively

The non-inferiority margin will be set to 1%. The calculation of percentage of time in a specified range is described in Section 7.4.2 of this document. If the upper bound of the one-sided 95% confidence interval for the least squares means difference between treatment groups at 13 weeks (μ_I minus μ_C) is <1%, non-inferiority will be established.

5.1.4.3 Percentage of Time >180 mg/dL

The hypotheses associated with this endpoint are:

- H_0: $\mu_I - \mu_C = 0$
- H_A: $\mu_I - \mu_C \neq 0$
  where μ_I and μ_C are the population means of per-participant percentage of time >180 mg/dL during the 13 weeks in the Intervention and Control groups, respectively.

The calculation of percentage of time in a specified range is described in Section 7.4.2 of this document. This endpoint will be considered met if the least squares means estimate of the difference between treatment groups at 13 weeks in the RLMM is significant at a two-sided significance level of 5%.

5.1.4.4 Percentage of Time >300 mg/dL

The hypotheses associated with this endpoint are:

- H_0: $\mu_I - \mu_C = 0$
- H_A: $\mu_I - \mu_C \neq 0$
  where μ_I and μ_C are the population means of per-participant percentage of time >300 mg/dL during the 13 weeks in the Intervention and Control groups, respectively.

The calculation of percentage of time in a specified range is described in Section 7.4.2 of this document. This endpoint will be considered met if the least squares means estimate of the difference between treatment groups at 13 weeks in the RLMM is significant at a two-sided significance level of 5%.

5.1.4.5 Percentage of Time <70 mg/dL (Non-inferiority)

The hypotheses associated with this endpoint are:

- H_0: $\mu_I - \mu_C \geq 1\%$
- H_A: $\mu_I - \mu_C < 1\%$
  where μ_I and μ_C are the population means of per-participant percentage of time <70 mg/dL during the 13 weeks in the Intervention and Control groups, respectively.

The non-inferiority margin will be set to 1%. The calculation of percentage of time in a specified range is described in Section 7.4.2 of this document. If the upper bound of the one-sided 95% confidence interval for the least squares means difference between treatment groups at 13 weeks (μ_I minus μ_C) is <1%, non-inferiority will be established.

5.1.4.6 Change from Baseline in HbA1c for Participants ≥18 Years of Age at Baseline

The hypotheses associated with this endpoint are:

- H_0: $\mu_I - \mu_C = 0$
- H_A: $\mu_I - \mu_C \neq 0$
  where μ_I and μ_C are the population means of change from baseline in HbA1c at 13 weeks for participants ≥18 years of age at baseline in the Intervention and Control groups, respectively.

The calculation of change from baseline in HbA1c is described in Section 7.4.1 of this document. This endpoint will be considered met if the least squares means estimate of the difference between treatment groups in the LMM is significant at a two-sided significance level of 5%.

5.1.4.7 Change from Baseline in HbA1c for Participants <18 Years of Age at Baseline

The hypotheses associated with this endpoint are:

- H_0: $\mu_I - \mu_C = 0$
- H_A: $\mu_I - \mu_C \neq 0$
  where μ_I and μ_C are the population means of change from baseline in HbA1c at 13 weeks for participants <18 years of age at baseline in the Intervention and Control groups, respectively.

The calculation of change from baseline in HbA1c is described in Section 7.4.1 of this document. This endpoint will be considered met if the least squares means estimate of the difference between treatment groups in the LMM is significant at a two-sided significance level of 5%.

5.1.4.8 Percentage of Time in Range (TIR) 70-180 mg/dL for Participants ≥18 Years of Age at Baseline

The hypotheses associated with this endpoint are:

- H_0: $\mu_I - \mu_C = 0$
- H_A: $\mu_I - \mu_C \neq 0$

  where μ_I and μ_C are the population means of percentage of time in range (TIR) 70-180 mg/dL during the 13 weeks for participants ≥18 years of age at baseline in the Intervention and Control groups, respectively.

The calculation of percentage of time in a specified range is described in Section 7.4.2 of this document. This endpoint will be considered met if the least squares means estimate of the difference between treatment groups at 13 weeks in the RLMM is significant at a two-sided significance level of 5%.

5.1.4.9 Percentage of Time in Range (TIR) 70-180 mg/dL for Participants <18 Years of Age at Baseline

The hypotheses associated with this endpoint are:

- H_0: $\mu_I - \mu_C = 0$
- H_A: $\mu_I - \mu_C \neq 0$

  where μ_I and μ_C are the population means of percentage of time in range (TIR) 70-180 mg/dL during the 13 weeks for participants <18 years of age at baseline in the Intervention and Control groups, respectively.

The calculation of percentage of time in a specified range is described in Section 7.4.2 of this document. This endpoint will be considered met if the least squares means estimate of the difference between treatment groups at 13 weeks in the RLMM is significant at a two-sided significance level of 5%.

5.1.4.10 Change from Baseline in HbA1c in Participants with Baseline HbA1c ≥8%

The hypotheses associated with this endpoint are:

- H_0: $\mu_I - \mu_C = 0$
- H_A: $\mu_I - \mu_C \neq 0$

  where μ_I and μ_C are the population means of change from baseline in HbA1c in participants with baseline HbA1c ≥8% at 13 weeks in the Intervention and Control groups, respectively.

The calculation of change from baseline in HbA1c is described in Section 7.4.1 of this document. This endpoint will be considered met if the least squares means estimate of the difference between treatment groups in the LMM is significant at a two-sided significance level of 5%.

5.1.4.11 Change from Baseline in PSQI Total Score

The hypotheses associated with this endpoint are:

- H_0: $\mu_I - \mu_C = 0$
- H_A: $\mu_I - \mu_C \neq 0$

where μ_I and μ_C are the population means of change from baseline in PSQI total score at 13 weeks in the Intervention and Control groups, respectively; change from baseline is calculated as follows:

The Pittsburgh Sleep Quality Index (PSQI) is further described in Section 7.7 of this document. This endpoint will be considered met if the least squares means estimate of the difference between treatment groups in the LMM is significant at a two-sided significance level of 5%. Change from baseline is calculated as follows:

$$Change\ from\ Baseline\ in\ PSQI = PSQI\ (Visit\ 9) - PSQI\ (Visit\ 3)$$

This endpoint will utilize the following versions of the PSQI questionnaire for the age cohorts:

- Children <12 y/o: Caregiver's version of the PSQI for Children
- Children ≥12 y/o: Self-reported version of the PSQI for Children
- Adults ≥18 y/o: Self-reported version of the PSQI for Adults.

5.1.4.12 Change from Baseline in T1-DDS Total Score

The hypotheses associated with this endpoint are:

- H_0: $\mu_I - \mu_C = 0$
- H_A: $\mu_I - \mu_C \neq 0$

  where μ_I and μ_C are the population means of change from baseline in T1-DDS total score at 13 weeks in the Intervention and Control groups, respectively; change from baseline is calculated as follows:

The Type-1 Diabetes Distress Scale is further described in Section 7.7 of this document. This endpoint will be considered met if the least squares means estimate of the difference between treatment groups in the LMM is significant at a two-sided significance level of 5%. Change from baseline in T1-DDS is calculated as follows:

$$Change\ from\ Baseline\ in\ T1DDS = T1DDS\ (Visit\ 9) - T1DDS\ (Visit\ 3)$$

5.1.4.13 Change from Baseline in Hypoglycemia Confidence Scale (HCS) Total Score

The hypotheses associated with this endpoint are:

- H_0: $\mu_I - \mu_C = 0$
- H_A: $\mu_I - \mu_C \neq 0$

  where μ_I and μ_C are the population means of change from baseline in HCS total score at 13 weeks in the Intervention and Control groups, respectively.

The Hypoglycemia Confidence Scale (HCS) is further described in Section 7.7 of this document. This endpoint will be considered met if the least squares means estimate of the difference between treatment groups in the LMM is significant at a two-sided significance level of 5%. Change from baseline is calculated as follows:

$$Change\ from\ Baseline\ in\ HCS = HCS\ (Visit\ 9) - HCS\ (Visit\ 3)$$

5.1.4.14 Percentage of Time <70 mg/dL

The hypotheses associated with this endpoint are:

- H_0: $\mu_I - \mu_C = 0$
- H_A: $\mu_I - \mu_C \neq 0$
  where μ_I and μ_C are the population means of percentage of time <70 mg/dL during the 13 weeks in the Intervention and Control groups, respectively.

The calculation of percentage of time in a specified range is described in Section 7.4.2 of this document. This endpoint will be considered met if the least squares means estimate of the difference between treatment groups at 13 weeks in the RLMM is significant at a two-sided significance level of 5%.

5.1.4.15 Percentage of Participants Achieving HbA1c <7%

The hypotheses associated with this endpoint are:

- H_0: $\pi_I - \pi_C = 0$
- H_A: $\pi_I - \pi_C \neq 0$
  where π_I and π_C are the population proportions of participants achieving HbA1c <7% at 13 weeks in the Intervention and Control groups, respectively.

This endpoint will be considered met if the least squares means estimate of the difference between treatment groups at 13 weeks in the logistic regression is significant at a two-sided significance level of 5%.

5.1.4.16 Change from Baseline in EQ-5D-3L Index Score

The hypotheses associated with this endpoint are:

- H_0: $\mu_I - \mu_C = 0$
- H_A: $\mu_I - \mu_C \neq 0$
  Where μ_I and μ_C are the population means of change from baseline in EQ-5D-3L index score at 13 weeks in the Intervention and Control groups, respectively.

The EQ-5D-3L instrument is further described in Section 7.7 of this document. This endpoint will be considered met if the least squares means estimate of the difference between treatment groups in the LMM is significant at a two-sided significance level of 5%. Change from baseline is calculated as follows:

$$Change\ from\ Baseline\ in\ EQ5D = EQ5D\ (Visit\ 9) - EQ5D\ (Visit\ 3)$$

This endpoint will utilize the following versions of the EQ-5D-3L questionnaire for the age cohorts:

- Children <16 y/o: Proxy version of the EQ-5D-3L for Children

- Children ≥16 y/o: Self-reported version of the EQ-5D-3L for Children
- Adults ≥18 y/o: Self-reported version of the EQ-5D-3L for Adults.

5.1.4.17 Change from Baseline in Total Daily Insulin (TDI) (units/kg) for Participants ≥18 Years of Age at Baseline

The hypotheses associated with this endpoint are:

- H_0: $\mu_I - \mu_C = 0$
- H_A: $\mu_I - \mu_C \neq 0$
  Where μ_I and μ_C are the population means of change from baseline in total daily insulin (units/kg) during the 13 weeks in the Intervention and Control groups, respectively.

The calculation of change from baseline in TDI is described in Section 7.4.4 of this document. This endpoint will be considered met if the least squares means estimate of the difference between treatment groups in the LMM is significant at a two-sided significance level of 5%.

5.1.4.18 Percentage of Time <54 mg/dL

The hypotheses associated with this endpoint are:

- H_0: $\mu_I - \mu_C = 0$
- H_A: $\mu_I - \mu_C \neq 0$
  where μ_I and μ_C are the population means of percentage of time <54 mg/dL during the 13 weeks in the Intervention and Control groups, respectively.

The calculation of percentage of time in a specified range is described in Section 7.4.2 of this document. This endpoint will be considered met if the least squares means estimate of the difference between treatment groups in the LMM is significant at a two-sided significance level of 5%.

5.2 ANALYSIS OF EXPLORATORY ENDPOINTS

List of exploratory endpoints is provided in Section 3.3 of this document.

5.2.1 Analysis Methods for Exploratory Endpoints

The mITT analysis set will be the main analysis set used to analyze these endpoints. Summary statistics will be presented for all endpoints and may be stratified by time points (e.g., day, night, overall) and age cohort (e.g., total, participants <18 years of age, and participants ≥18 years of age) of interest if appropriate.

5.2.1.1 Period 1 – 13-week Randomized Period

Exploratory endpoints will be analyzed as in Section 5.1 for the Period 1 – 13-week Randomized Period.

False Discovery Rate for Multiple Testing of Exploratory Endpoints

To control for False Discovery Rate (FDR) among the randomized period exploratory endpoints the Benjamini-Yekutieli (2001)[5] method for multiple testing will be implemented to the groups of exploratory endpoints below.

Briefly, the Benjamini-Yekutieli procedure is a step-up testing procedure that do not assume any hierarchy among the tested null hypotheses. The procedure ranks the p-values and compares the largest p-value to the largest endpoint-specific critical value (α). If the largest p-value does not show statistical significance, testing proceeds to compare the second-largest p-value to the second-largest adjusted alpha value. Sequential testing continues in this manner until a p-value for an endpoint is statistically significant, whereupon the provides a conclusion of statistically significant treatment effects for that endpoint and all endpoints with smaller p-values.

Each family of endpoints listed below will be analyzed separately so that FDR is controlled at 5% within each family.

Family #1: Glycemic Measures; Reduction of Hypoglycemia

1. Percentage of time <54 mg/dL (3.0 mmol/L) for participants <18 years of age at baseline
2. Percentage of time <54 mg/dL (3.0 mmol/L) for participants ≥18 years of age at baseline
3. Percentage of time <70 mg/dL (3.9 mmol/L) for participants <18 years of age at baseline
4. Percentage of time <70 mg/dL (3.9 mmol/L) for participants ≥18 years of age at baseline
5. Percentage of time <70 mg/dL (3.9 mmol/L) during Daytime
6. Percentage of time <70 mg/dL (3.9 mmol/L) during Nighttime
7. Coefficient of variation (%)
8. Coefficient of variation (%) for participants <18 years of age at baseline
9. Coefficient of variation (%) for participants ≥18 years of age at baseline
10. Number of hypoglycemic events as measured by the glucose sensor (<70 mg/dL for 15 minutes)
11. Number of hypoglycemic events as measured by the glucose sensor (<70 mg/dL for 15 minutes) for participants <18 years of age at baseline
12. Number of hypoglycemic events as measured by the glucose sensor (<70 mg/dL for 15 minutes) for participants ≥18 years of age at baseline
13. Number of hypoglycemic events as measured by the glucose sensor (<54 mg/dL for 15 minutes)
14. Number of hypoglycemic events as measured by the glucose sensor (<54 mg/dL for 15 minutes) for participants <18 years of age at baseline

[5] Benjamini, Y., & Yekutieli, D. (2001). The Control of the False Discovery Rate in Multiple Testing under Dependency. The Annals of Statistics, 29(4), 1165–1188. http://www.jstor.org/stable/2674075.

15. Number of hypoglycemic events as measured by the glucose sensor (<54 mg/dL for 15 minutes) for participants ≥18 years of age at baseline

Family #2: Glycemic Measures; Reduction of Hyperglycemia

1. Change from baseline in A1c in France participants
2. Change from baseline in A1c in United Kingdom participants
3. Percentage of time in range 70-180 mg/dL (3.9-10.0 mmol/L) during Daytime
4. Percentage of time in range 70-180 mg/dL (3.9-10.0 mmol/L) during Nighttime
5. Mean glucose (mg/dL and mmol/L)
6. Mean glucose (mg/dL and mmol/L) for participants <18 years of age at baseline
7. Mean glucose (mg/dL and mmol/L) for participants ≥18 years of age at baseline
8. Percentage of time >180 mg/dL (10.0 mmol/L) for participants <18 years of age at baseline
9. Percentage of time >180 mg/dL (10.0 mmol/L) for participants ≥18 years of age at baseline
10. Percentage of time >250 mg/dL (13.9 mmol/L)
11. Percentage of time >250 mg/dL (13.9 mmol/L) for participants <18 years of age at baseline
12. Percentage of time >250 mg/dL (13.9 mmol/L) for participants ≥18 years of age at baseline
13. Percentage of time >300 mg/dL (16.7 mmol/L) for participants <18 years of age at baseline
14. Percentage of time >300 mg/dL (16.7 mmol/L) for participants ≥18 years of age at baseline
15. Number of hyperglycemia events as measured by the glucose sensor (≥300 mg/dL for 1 hour)
16. Number of hyperglycemia events as measured by the glucose sensor (≥300 mg/dL for 1 hour) for participants <18 years of age at baseline
17. Number of hyperglycemia events as measured by the glucose sensor (≥300 mg/dL for 1 hour) for participants ≥18 years of age at baseline
18. Percentage of participants in range 70-180 mg/dL (3.9-10.0 mmol/L) >70% of time
19. Percentage of children (<18 years of age at baseline) participants in range 70-180 mg/dL (3.9-10.0 mmol/L) >70% of time
20. Percentage of adult (≥18 years of age at baseline) participants in range 70-180 mg/dL (3.9-10.0 mmol/L) >70% of time
21. Percentage of participants in range 70-180 mg/dL (3.9-10.0 mmol/L) >70% of time and below range <70 mg/dL (3.9 mmol/L) (TBR) <4% of time
22. Percentage of children (<18 years of age at baseline) participants in range 70-180 mg/dL (3.9-10.0 mmol/L) >70% of time and below range <70 mg/dL (3.9 mmol/L) (TBR) <4% of time
23. Percentage of adult (≥18 years of age at baseline) participants in range 70-180 mg/dL (3.9-10.0 mmol/L) >70% of time and below range <70 mg/dL (3.9 mmol/L) (TBR) <4% of time
24. Percentage of participants achieving A1c <6.5% (48 mmol/mol)

25. Percentage of children (<18 years of age at baseline) participants achieving A1c <6.5% (48 mmol/mol)
26. Percentage of adults (≥18 years of age at baseline) participants achieving A1c <6.5% (48 mmol/mol)
27. Percentage of children (<18 years of age at baseline) participants achieving A1c <7% (53 mmol/mol)
28. Percentage of adults (≥18 years of age at baseline) participants achieving A1c <7% (53 mmol/mol)

Family #3: Clinical Metrics (Insulin, BMI)

1. Change from baseline in total daily insulin (TDI) (units/kg) for participants <18 years of age at baseline
2. Change from baseline in total daily insulin (TDI) (units) for participants <18 years of age at baseline
3. Change from baseline in total daily insulin (TDI) (units) for participants ≥18 years of age at baseline
4. Change from baseline in Body Mass Index (BMI) z-score for participants <18 years of age at baseline
5. Change from baseline in Body Mass Index (BMI) (kg/m^2) for participants ≥18 years of age at baseline

Family #4: Questionnaires

1. Change from baseline in PSQI total score for caregivers of pediatric subjects
2. Change from baseline in PSQI total score for caregivers of teen subjects
3. Change from baseline in PSQI total score for teen subjects
4. Change from baseline in PSQI total score for adult subjects
5. Change from baseline in PSQI overall sleep quality subscale for caregivers of pediatric subjects
6. Change from baseline in PSQI overall sleep quality subscale for caregivers of teen subjects
7. Change from baseline in PSQI overall sleep quality subscale for teen subjects
8. Change from baseline in PSQI overall sleep quality subscale for adult subjects
9. Change from baseline in PSQI sleep duration subscale for caregivers of pediatric subjects
10. Change from baseline in PSQI sleep duration subscale for caregivers of teen subjects
11. Change from baseline in PSQI sleep duration subscale for teen subjects
12. Change from baseline in PSQI sleep duration subscale for adult subjects
13. Change from baseline in HCS total score for caregivers of pediatric subjects
14. Change from baseline in HCS total score for caregivers of teen subjects
15. Change from baseline in HCS total score for teen subjects
16. Change from baseline in EQ-5D-3L VAS score
17. Change from baseline in DQOL Brief for adult subjects
18. Change from Baseline in SUS for caregivers of pediatric subjects (Omnipod 5 Only)
19. Change from Baseline in SUS for caregivers of teen subjects (Omnipod 5 Only)
20. Change from Baseline in SUS for teen subjects (Omnipod 5 Only)

21. Change from Baseline in SUS for adult subjects (Omnipod 5 Only)
22. Days missed from work or left early/late for adults
23. Days missed from school or left early/late for teenagers
24. Days missed from work or left early/late for caregivers of teenagers
25. Days missed from work or left early/late for caregivers of children
26. Proportion of participants achieving a Total Score > 5 (Poor Sleepers) on the PSQI questionnaire at 13 weeks.
27. Proportion of participants achieving a minimally clinically important difference (MCID) of ≥0.19 points (improvement) on the T1-DDS questionnaire total score at 13 weeks.
28. Proportion of participants achieving MCID score of ≥ 3 on the HCS questionnaire at 13 weeks for participants ≥18 years of age at baseline

5.2.1.2 Period 1 – 13-week Extension Period

Exploratory endpoints for Extension Period 1 will be evaluated at the end of the 13-week Extension Period and compared to the start of the Omnipod 5 System use, either at the end of 26 weeks for the Intervention group as compared to baseline, or at the end of 26 weeks compared to the end of 13-week randomized period for the Control group.

Continuous endpoints will be analyzed using a paired t-test between the start and end of Omnipod 5 System use within each group separately. Normality of the differences will be assessed, and if the data are highly skewed, the Wilcoxon Signed-Rank Test will be employed as a non-parametric alternative. Binary endpoints will be evaluated using McNemar's Test to assess paired proportions.

No imputation for missing data will be performed for the analysis of 13-week extension endpoints. No control for multiplicity testing will be performed; all p-values will be considered exploratory.

5.2.2 Episodes of Severe Hypoglycemia and Diabetic Ketoacidosis

The number of severe hypoglycemia and DKA (diabetic ketoacidosis) adverse events, and the number and percent of subjects with at least one event in each group will be summarized.

As the number of episodes (events) of severe hypoglycemia and DKA are of significant interest, statistical testing will be performed for the rate of SH (and DKA) if there are ≥5 events (of SH or DKA, respectively) combined across both treatment groups. The rates will be calculated as the number of events per 100 person years. The rates will be compared using a Poisson regression with site as a random effect. The amount of follow-up will be included as an offset term. If there are concerns with model convergence (e.g., due to zero events in one group), Fisher's exact test for the number of events will be used instead.

6 ANALYSIS OF SAFETY

All adverse events reported during the study will be reviewed and adequately reported to comply with applicable regulations. All reportable AEs will be assessed by the investigator who will determine whether the event is related to the study procedures or related to the study device and whether the event meets any of the criteria for seriousness. The event will be considered serious if the event meets at least one criterion for seriousness. All safety analyses will be based on the mITT analysis set.

6.1 MEDICAL MONITOR

A Medical Monitor will be responsible for individual and timely review of adverse events, including serious adverse events (SAEs) and adverse device events. The Medical Monitor will conduct adjudication of any events of Diabetic Ketoacidosis (DKA) or Severe Hypoglycemia (SH) or any additional events as requested by the Sponsor. The specified events will be adjudicated to determine event relatedness to the study procedures and/or the devices (participant's own insulin pump, study CGM and Omnipod 5), and whether an adverse event is unanticipated. The adjudication decision of the Medical Monitor will be used for the final classification of events, including relatedness to the study procedures and/or the devices, for the determination of safety endpoints and for all regulatory reports, product labeling, and publications or presentations.

6.2 RELATIONSHIP TO STUDY DEVICE AND PROCEDURE

The causal relationship to the study procedures and the investigational device for each adverse event will be rated as follows:

- Unrelated: The event is not related to the procedures or the investigational device.
- Possibly Related: The temporal sequence is such that the relationship is not unlikely or there is no contradicting evidence that can reasonably explain the participant's condition. There is a possibility of any relation between the event and the procedures or the devices.
- Related: The temporal sequence is relevant, or the event abates upon completion of the procedure/ use of devices, or the event cannot be reasonably explained by the participant's condition or comorbidities. The event is related or most likely associated with the procedures or the devices.
- Causal Relationship: The serious event is associated with the investigational device or with procedures beyond reasonable doubt.

For the purposes of dichotomizing the causal relationship in safety summaries, events that are "Related", "Possibly Related" or have a "Causal Relationship" will be considered related.

6.3 SEVERITY

The severity of the adverse event will be rated based upon the following grades:

- Mild: Usually transient, requires no special treatment, and does not interfere with the participant's daily activities.
- Moderate: Usually causes a low level of inconvenience, discomfort or concern to the participant and may interfere with daily activities but is usually ameliorated by simple therapeutic measures and participant is able to continue in study.
- Severe: Interrupts a participant's usual daily activities, causes severe discomfort, may cause discontinuation of study device, and generally requires systemic drug therapy or other treatment.

6.4 OUTCOME

The outcome of each reportable adverse event will be classified by the investigator as follows:

- Recovered/Resolved: The participant recovered from the AE/SAE without sequelae.
- Recovered/Resolved with Sequelae: The event persisted and had stabilized without further anticipated change in the event status.
- Fatal: A fatal outcome is defined as the SAE that resulted in death. Only the event that was the cause of death should be reported as fatal. AEs/SAEs that were ongoing at the time of death; however, were not the cause of death, will be recorded as "resolved" at the time of death.
- Not Recovered/Not Resolved (Ongoing): An ongoing AE/SAE is defined as the event was ongoing with an undetermined outcome.
    - An ongoing outcome will require follow-up by the site in order to determine the final outcome of the AE/SAE or until participant completes the study.
    - The outcome of an ongoing event at the time of death that was not the cause of death, will be updated and recorded as "resolved" with the date of death recorded as the stop date.
- Unknown: An unknown outcome is defined as an inability to access the participant or the participant's records to determine the outcome (for example, a participant that was lost to follow-up).

If any Unanticipated Adverse Device Effects (UADEs) are ongoing when a participant completes the study (or withdraws), the participant will continue to be followed until the event resolves or has no prospect of improvement or change, even after the participant has completed all applicable study visits/contacts, unless that participant has withdrawn their consent. For all other reportable adverse events, data collection will end at the time the participant completes the study.

Note: Participants should continue to receive appropriate medical care for an adverse event after their participation in the study ends.

6.5 ANALYSIS OF ADVERSE EVENTS

All adverse events reported over the course of the study will be summarized and tabulated by study phase (standard therapy through end of study), event category, seriousness, severity, and relationship to the study procedure and the devices. For the purposes of summarization, an event will be considered “Related” if the relationship was deemed as “Possibly Related”, “Related” or have a “Causal Relationship”. In cases where the same event is reported more than once per participant, the event will only be counted once in the incidence table(s).

Adverse events leading to death or to discontinuation from the study will be listed separately. A listing of all adverse events will be provided. Adverse events reported for subjects excluded from mITT will be listed separately.

6.6 EVALUATION OF DEVICE DEFICIENCIES

Device deficiencies will be tabulated and listed in a manner similar to the methods described for adverse events. Any device deficiency with potential to cause a Serious Adverse Event, leading to an adverse event, or leading to study termination will be listed separately.

7 GENERAL STATISTICAL CONSIDERATIONS

7.1 VISIT AND ANALYSIS WINDOWS

CGM data will be included in the analysis through the specific visit as reported on the appropriate eCRF, and not necessarily through the optimal visit date. The nominal visit interval as reported on the appropriate eCRF will be used for analysis of HbA1c, PROs, and other outcomes recorded or collected during the office/telephone visits. Missing 13-week HbA1c and PRO data can be included in the analysis as long as the data was collected within the specific analysis window (as further described in Section 7.6 of this document).

7.2 ANALYSIS SETS

The following analysis sets are planned for the study:

7.2.1 ITT (Intention to Treat) Analysis Set

The ITT analysis set includes all participants that are enrolled in the study.

7.2.2 mITT (modified Intention to Treat) Analysis Set

The modified Intention to Treat (mITT) analysis set is a subset of the ITT analysis set. The mITT analysis set will consist of all participants who have been randomized. The mITT analysis set will be used as the primary analysis for the primary, secondary and endpoints and for other clinical outcome data.

7.2.3 PP (Per Protocol) Analysis Set

The Per-Protocol (PP) analysis set is a subset of the mITT analysis set. Participants will be included in the PP analysis set if they have a minimum of 70% system use as measured by the study sensor (Control group) or Omnipod 5 (Intervention group) during the 13-week randomization period over a minimum duration of 10 weeks and have completed the study without major protocol deviations. The PP analysis set will be used as supportive analysis for the endpoints.

To meet the minimum data requirement for inclusion in the PP analysis set, the subject must meet both of the following criteria:

1. Minimum duration of randomized period of 10 weeks (70 days); see Section 7.5.2 for calculation of non-CGM derived randomized period

2. ⩾70% of system use during the randomized period; this is calculated as

   - For subjects randomized to Omnipod 5:

$$\left(\frac{number\ of\ OP5\ records}{288}\right) \div (length\ of\ non-CGM\ randmized\ period\ in\ days) \geq 0.7$$

   - For subjects randomized to Control:

$$\left(\frac{number\ of\ Libre\ records}{96}\right) \div (length\ of\ non-CGM\ randmized\ period\ in\ days) \geq 0.7$$

For Omnipod 5, all records inclusive of error codes are included.

The following will be considered major protocol deviations:

- Major inclusion/exclusion criterion deviation
- Significant protocol non-compliance that may confound the study objective data (e.g., use of prohibited medications, not using control group (MDI therapy) for prolonged period)

The list of participants excluded from the PP analysis set will be determined prior to analysis. If the PP analysis set does not differ from the mITT analysis set, separate analyses will not be presented.

7.3 CONTROL OF SYSTEMATIC BIAS

Several measures are incorporated into the study design to help minimize study bias as follows:

1) This is a prospective, randomized, parallel-group multi-center study to help ensure that investigator or site or subject enrollment bias is minimized. Selection of

participants will be made from the Investigator's usual subject load. Consecutively eligible subjects should be enrolled into the study.

2) This document specifies appropriate statistical methodology to ensure that bias is minimized.
3) The effectiveness measures will be based on the direct output from the device or are analyzed at a National Glycohemoglobin Standardization Program (NGSP) certified central laboratory, ensuring objective reporting.
4) A Medical Monitor will adjudicate all SAEs and device-related adverse events to ensure consistency across all evets; the Medical Monitor's assessment of adverse events will be used for regulatory reports, product labeling, and publications or presentation.

7.4 CALCULATION OF ENDPOINT OUTCOMES

7.4.1 Change from Baseline in HbA1c

Change from baseline in HbA1c at 13 weeks will be compared between groups. The data will be collected at Visit 1 (Screening) and at Visit 9 (13 weeks), as well as Visit 15 (Day 180 during the extension phase). Change from baseline in HbA1c is calculated as follows:

$$Change\ from\ Baseline\ in\ HbA1c = HbA1c\ (follow-up) - \ HbA1c\ (Visit\ 1)$$

7.4.2 Calculation of Percentage of Time

Several effectiveness endpoints involve calculation of percentage of time in a specific glycemic range. These endpoints will be based on the direct output from a device, either the Continuous Glucose Monitoring (CGM) device (Abbott FreeStyle Libre 2 Glucose Sensor, "FreeStyle Libre 2") or Omnipod 5. The percentage of time in a specified range (e.g., TIR) will be calculated per participant as follows:

$$100 \times \frac{\#\ of\ CGM\ readings\ in\ a\ specified\ range}{\#\ of\ evaluable\ CGM\ readings}$$

The following CGM readings will be excluded from analysis, and therefore, from calculation of TIR endpoints:

- No glucose value is provided in the device output, such as due to an error or device deficiency during which the device does not record glucose readings
- CGM readings reported prior to start of the applicable period, or after the end of the applicable period (e.g., no readings prior to start of the randomized period will be included in the analysis of TIR during randomized period)

7.4.3 Change from Baseline in Body Mass Index (BMI)

Change from Baseline in BMI at 13 weeks will be compared between groups. Height is collected at Visit 1 (Screening); weight is collected at Visit 1 and at Visit 9 (13 weeks). Change in BMI is calculated as follows:

$$Change\ from\ Baseline\ in\ BMI = BMI\ (13\ weeks) - BMI\ (Visit\ 1)$$

where BMI at baseline (Visit 1) is calculated as:

$$BMI\ (Visit\ 1) = \frac{Weight\ at\ Visit\ 1\ (kg)}{(Height\ at\ Visit\ 1\ (m))^2}$$

and BMI at 13 weeks (Visit 9) is calculated as:

$$BMI\ (13\ weeks) = \frac{Weight\ at\ 13\ weeks\ (kg)}{(Height\ at\ Visit\ 1\ (m))^2}$$

If a subject's weight is reported in pounds, the following conversion will be performed:

$$Weight\ (kg) = \frac{Weight\ (lbs)}{2.2}$$

If a subject's height is reported in inches, the following conversion will be performed:

$$Height\ (m) = \frac{Height\ (in) * 2.54}{100}$$

BMI for children (age <18 years) will be converted to z-score based on the SAS program provided by the U.S. Center for Disease Control and Prevention (CDC)[6].

7.4.4 Change from Baseline in Total Daily Insulin (TDI)

Change from Baseline in TDI (units/kg) at the end of the 13-week randomized period will be compared between groups. The insulin requirements will be collected at Visit 2 (Standard Therapy) and at Visit 9 (13 weeks randomized period), and change in TDI will be calculated as follows:

$$TDI\ (change\ from\ Baseline, units/kg) = \frac{TDI\ (13\ weeks) - TDI\ (Visit\ 2)}{subject's\ weight\ at\ Visit\ 1}$$

7.4.5 Additional CGM-Derived Endpoints

Additional CGM-derived endpoints, such as coefficient of variation (CV), percentage of time >250 mg/dL, percentage of time <54 mg/dL, TIR during daytime and nighttime hours will be compared between groups at the end of the 13-week randomized period.

CV is calculated per subject as follows, then summarized and compared between groups:

$$CV(\%) = \frac{SD\ of\ glucose}{mean\ glucose}$$

[6] The SAS Program for CDC Growth Charts that Includes the Extended BMI Calculations. https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm

7.4.6 Hypoglycemia and Hyperglycemia Events

7.4.6.1 Down-Sampling

The number of hypoglycemia and hyperglycemia events will be based on the data obtained from the glucose sensor. As the Libre device reports glycemic values every ~15 minutes, and the Omnipod 5 device reports glycemic values every ~5 minutes, the glycemic readings obtained from Omnipod 5 will be "down-sampled" to match the frequency of readings from the Libre device. This "down-sampling" will only be applied for the calculation of the number of hyperglycemia and hypoglycemia events; all Omnipod 5 readings will be used in the assessment of other glycemic measures.

The "down-sampling" of Omnipod 5 data will be performed as follows:

1. The readings within the relevant analysis period (e.g., randomized period) are sorted by local time for each subject.
2. The first reading for the subject will be included in analysis.
3. The time of the second reading will be compared to the time of the first reading that was included in analysis.
    a. If the readings are <13 minutes apart, the second reading will not be included in analysis.
    b. If the readings are ≥13 minutes apart, the second reading will be included in analysis.
4. The time of the third reading will be compared to the time of the most recent reading that was included in analysis.
    a. If the readings are <13 minutes apart, the third reading will not be included in analysis.
    b. If the readings are ≥13 minutes apart, the third reading will be included in analysis.

This process will continue until all Omnipod 5 readings from the relevant analysis period have been assessed for inclusion in analysis. Allowing each subsequent Omnipod 5 reading to be no less than 13 minutes from the previous reading that is included in analysis will ensure the same frequency of reported values between the two devices.

7.4.6.2 Number of Hypoglycemia Events

This endpoint will be assessed separately using <70 mg/dL and <54 mg/dL as definitions of hypoglycemia for ≥ 15 minutes. Therefore, a hypoglycemia event will be recorded if two consecutive readings are in hypoglycemic range (either <70 mg/dL or <54 mg/dL, depending on endpoint) with the difference between the two readings 13-17 minutes, inclusive. The subject will be eligible for a new event when no hypoglycemia readings have occurred for 41 minutes (equivalent to two consecutive readings above the hypoglycemia range).

7.4.6.3 Number of Hyperglycemia Events

This endpoint is defined as glucose sensor values ≥300 mg/dL for ≥1 hour. Therefore, a hyperglycemia event will be recorded if four consecutive readings are in hyperglycemic range (≥300 mg/dL) with the difference between the first and the last reading 56-64 minutes, inclusive. The subject will be eligible for a new event when no hyperglycemia readings have occurred for 71 minutes (equivalent to four consecutive readings below the hyperglycemia range).

7.5 LENGTH OF STUDY PERIODS

For certain analysis, it may be needed to calculate the length of the study period. The length of study period is calculated as the difference between the start and the end of study period. CGM derived and Non-CGM derived endpoints will require different definitions for start and end of study periods based on the availability of data collected. Start and end of study periods period are defined below.

7.5.1 CGM Endpoints

CGM data are collected continuously throughout the study.

The period for CGM data collection is defined as follows for the subjects in the Intervention group:

Period	Start Date/Time	End Date Time

13-week randomized period (Period 1)	• Earlier of the first non-error CGM reading using Omnipod 5, or Date/Time participant entered automated mode at Visit 4.	• Subjects continuing into 13-week extension.
		  ○ Noon on the day of Visit 9
		• Subjects not continuing into 13-week extension.
		  ○ Earlier of (1) the last non-error CGM reading using Omnipod 5, on or prior to the date the Controller was returned to the site, or (2) the last non-error CGM reading using Omnipod 5 on the date of study exit visit (Visit 9).

13-week extension (Period 1)	• One second after noon (12:00:01) on the day of Visit 9	• Subjects continuing into extension through commercialization
		  ○ Noon on the day of Visit 15
		• Subjects not continuing into extension through commercialization
		  ○ Earlier of (1) the last non-error CGM reading using Omnipod 5, on or prior to the date the Controller was returned to the site, or (2) the last non-error CGM reading using Omnipod 5 on the date of study exit visit (Visit 15)

Extension through commercialization (Period 2)	• One second after noon (12:00:01) on the day of Visit 15	• Earlier of (1) the last non-error CGM reading using Omnipod 5, on or prior to the date the Controller was returned to the site, or (2) the last non-error CGM

Period	Start Date/Time	End Date Time
		reading using Omnipod 5 on the date of study exit visit

The period for CGM data collection is defined as follows for the subjects in the Control group:

Period	Start Date/Time	End Date Time

13-week randomized period (Period 1)	• Noon on the day of Visit 4	• Subjects continuing into 13-week extension.
		  ○ The last CGM reading using Libre sensor prior to the start of the 13-week extension.
		• Subjects not continuing into 13-week extension.
		  ○ The last CGM reading using Libre sensor on the date of study exit visit (Visit 9)

13-week extension (Period 1)	• Earlier of (1) the first non-error CGM reading using Omnipod 5, or (2) Date/Time participant entered automated mode at Visit 10	• Subjects continuing into extension through commercialization
		  ○ Noon on the day of Visit 15
		• Subjects not continuing into extension through commercialization
		  ○ Earlier of (1) the last non-error CGM reading using Omnipod 5, on or prior to the date the Controller was returned to the site, or (2) the last non-error CGM reading using Omnipod 5 on the date of study exit visit (Visit 15)

Extension through commercialization (Period 2)	• One second after noon (12:00:01) on the day of Visit 15	• Earlier of (1) the last non-error CGM reading using Omnipod 5, on or prior to the date the Controller was returned to the site, or (2) the last non-error CGM reading using Omnipod 5 on the date of study exit visit

7.5.2 Non-CGM Endpoints

Start and end of study periods for non-CGM endpoints (e.g., HbA1c, safety analyses) will be based on the protocol definitions for start of study periods regardless of randomization (or treated) arm. Start and end of study periods period are defined below.

Period	Start Date/Time	End Date Time
13-week randomized period (Period 1)	• Date of Visit 3.	• Date of Visit 9.
13-week extension (Period 1)	• 1 day following Date of Visit 9.	• Date of Visit 15.

Period	Start Date/Time	End Date Time
Extension through commercialization	• 1 day following Date of Visit 15.	• Date of Study Exit Visit

7.6 HANDLING OF MISSING DATA

7.6.1. Missing Data Handling for HbA1c/PRO

It is likely that at least some participants do not contribute data for the primary endpoint (change in HbA1c) or patient-reported outcome endpoints (e.g., due to early withdrawal). For the main analysis of change in HbA1c/PRO, missing values for the participants in the mITT analysis set will be imputed as follows:

- If a participant withdrew from the study early and provided HbA1c/PRO value collected within 13±2 weeks from start of the 13-week randomized period, the last known HbA1c/PRO values will be imputed for change in HbA1c/PRO data endpoint.
- If a participant is confirmed to have withdrawn early from the study due to unsatisfactory treatment or potential loss of efficacy outside of the 13±2 weeks window, the change in HbA1c/PRO data endpoint will be assumed to be zero (e.g., no change).
- If a participant does not provide a value for change in HbA1c/PRO for other reason (e.g., lost sample, participant lost to follow-up), the change in HbA1c/PRO data endpoint will be imputed using multiple imputation.

Missing data will be handled using multiple imputation assuming missing at random (MAR). The imputation model will include change from baseline for the PRO score or HbA1c value at 13 weeks, treatment group, baseline value, age, sex, and duration of diagnosis. Multiple imputation will involve the following steps:

1. Generate 100 imputed data sets.
2. Fit the mixed effects linear regression model on each imputed dataset. Calculate the point estimate and standard error of the treatment group difference for each imputed dataset.
3. Pool the estimates across imputations to get an overall point estimate and confidence interval for the treatment group difference.

7.6.2. Missing Data Handling for CGM-derived Endpoints

Due to the nature of the data and study design, it is anticipated that all randomized participants will contribute at least some sensor data post-randomization. Hence, it is possible that there will be no need for imputation of missing values for these endpoints.

All randomized participant s (i.e., mITT analysis set) will provide an endpoint value for all secondary sensor-derived endpoints as follows:

- If a randomized participant provides at least seven days' worth of sensor readings (2,016 readings for Omnipod 5 system; and 672 readings for Libre sensor for Control subjects) during both the standard therapy and 13-week randomized period, all the available sensor readings will be collapsed (averaged) for a per-participant value for a specific CGM-derived endpoint.

- If a randomized participant does not provide at least seven days' worth of sensor readings (2,016 readings for Omnipod 5 system; and 672 readings for Libre sensor for Control subjects) during both the standard therapy and 13-week randomized period, the sensor readings for that participant will be excluded from analysis, and instead, a per-participant value for a specific CGM-derived endpoint will be handled as described in Section 5.1.2.

Gaps in sensor data, such as due to loss of signal, will not be imputed. Sensor values missing for other reasons will not be imputed. No additional imputations for missing data are planned for the endpoints involving sensor data.

No imputation for missing data is planned for the analysis of extension period endpoints or summaries.

7.7 PATIENT-REPORTED OUTCOMES

The following questionnaires will be used to evaluate general and disease and disease-specific quality of life, and device usability.

Type 1-Diabetes Distress Scale (T1-DDS)

The T1-DDS is a 28-item self-report instrument. Each item is rated on a 6-point scale from (1) "not a problem" to (6) "a very serious problem." The scale yields an overall distress score based on average responses along the 1-6 scale for all 28 items (range = 1-6). The scale also yields a score for each of seven subscales based on the average response on all of the items in that subscale (range = 1-6) [7].

T1-DDS is collected from adult subjects (aged 18-70 years) at Baseline (Visit 3) as well as at the end of 13 weeks (Visit 9), end of the extension period 1 (Visit 15), and end of extension period 2.

Hypoglycemia Confidence Scale (HCS)

[7] L. Fisher, W. H. Polonsky, D. M. Hessler, U. Masharani, I. Blumer, A. L. Peters, L. A. Strycker and V. Bowyer, "Understanding the sources of diabetes distress in adults with type 1 diabetes," J Diabetes Complications, vol. 29, no. 4, pp. 572-7, 2015.

The HCS is a nine-item self-report scale that examines the degree to which people with diabetes feel able, secure, and comfortable regarding their ability to stay safe from hypoglycemic-related problems. Each item is rated on a 4-point scale from (1) “not confident at all” to (4) “very confident”. The total score is calculated as the sum of each item divided by the number of items completed [8].

HCS is collected from subjects aged 12-70 years, and from caregivers of children aged 4 to <18 years at Baseline (Visit 3) as well as at the end of 13 weeks (Visit 9), end of the extension period 1 (Visit 15), and end of extension period 2.

Pittsburgh Sleep Quality Index (PSQI)

The PSQI is used to measure the quality and patterns of sleep, by measuring seven domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction over the last month. Responses are converted to a 0 to 3 scale, with higher scores indicating more negative quality of sleep. A global sum of >5 indicates a “poor” sleeper. The PSQI global score is calculated as the sum of the seven component scores [9] .

PSQI is collected from subjects aged 12-70 years, and from caregivers of children aged 4 to <18 years at Baseline (Visit 3) as well as at the end of 13 weeks (Visit 9) and at the end of the extension period 1 (Visit 15).

EQ-5D-3L

The EQ-5D-3L is a short, generic, validated quality-of-life instrument used to measure health outcomes. It consists of five dimensions (questions) regarding mobility, self-care, usual activities, pain/discomfort and anxiety/depression, and one visual analog scale to measure the subject’s self-rated health. Each of the five dimensions is divided into three levels of perceived problems: Level 1 indicating no problem, Level 2 indicating some problems, and Level 3 indicating extreme problems. Responses to five dimensions can be converted into a single summary index score [10]. Both, subject-completed version and proxy version, will be used in this study.

EQ-5D-3L, either subject-completed or proxy version, is collected from subjects aged 16-70 years, and from caregivers of children aged 4 to <18 years at Baseline (Visit 3) as well as at the end of 13 weeks (Visit 9) and at the end of the extension period 1 (Visit 15).

[8] W. H. Polonsky, L. Fisher, D. Hessler and S. V. Edelman, "Investigating Hypoglycemic Confidence in Type 1 and Type 2 Diabete," Diabetes Technol The, vol. 19, no. 1, pp. 1-6, 2017.
[9] D. Buysse, C. Reynolds, T. Monk, S. Berman and D. Kupfer, "The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research," Psychiatry Res, vol. 28, no. 2, pp. 193-213, 1989.
[10] R. Rabin and F. D. Charro, "EQ-SD: a measure of health status from the EuroQol Group," Annals of Medicine, vol. 33, no. 5, pp. 337-343, 2001.

The EQ VAS records the subject's self-rated health on a 0 to 100 scale. Missing values in the EQ VAS should be coded as "999" and ambiguous values (e.g., the line crosses the scale twice) should be treated as missing values.

Diabetes Quality of Life-brief (DQOL-brief)

The DQOL-brief is a 15-item instrument that provides a total quality-of-life score[11]. Each item is rated on a 5-point scale from (1) "Very Dissatisfied" or "All the Time" to (5) "Very Satisfied" or "Never." Respondents must answer at least ten (two thirds) questions to be included in the analysis. The DQOL total score is calculated by summing the scores for all items and dividing by the numbers of responses answered. Higher scores indicate a more positive quality of life.

DQOL-brief is collected from adult subjects (aged 18-70 years) at Baseline (Visit 3) as well as at the end of 13 weeks (Visit 9), end of the extension period 1 (Visit 15), and end of the extension period 2.

Clarke Hypoglycemia Awareness

Clarke Questionnaire is an eight-item questionnaire to assess reduced awareness of hypoglycemia[12]. Responses to each item are scored as "A" or "R" (or "U" which is equal to four "R" responses). Total of four or more "R" responses are considered to indicate reduced awareness. Generally, no missing data imputation will be performed, but it is possible in certain cases to determine whether or not a participant has reduced awareness, even in the presence of missing responses (e.g., participant is missing a single response, but if the participant only has two "R" responses for the remaining seven items, it can be concluded that the participant does not have reduced awareness since adding another "R" response would result in fewer than four "R"s).

Clarke Questionnaire is collected from subjects aged 12-70 years, and from caregivers of children aged 4 to <12 years at Baseline (Visit 3) as well as at the end of 13 weeks (Visit 9) and end of the extension period 1 (Visit 15).

System Usability Scale (SUS)

The SUS is a 10-item questionnaire constructed on a 5-point Likert scale, with responses ranging from (1) "Strongly disagree" to (5) "Strongly agree"[13]. It is not recommended that the individual items be scored, but rather a single composite

[11] Thomas E. Burroughs, Radhika Desikan, Brian M. Waterman, Debra Gilin, Janet McGill; Development and Validation of the Diabetes Quality of Life Brief Clinical Inventory. Diabetes Spectr 1 January 2004; 17 (1): 41–49. https://doi.org/10.2337/diaspect.17.1.41
[12] Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, Polonsky W. Reduced awareness of hypoglycemia in adults with IDDM. A prospective study of hypoglycemic frequency and associated symptoms. Diabetes Care. 1995 Apr;18(4):517-22. doi: 10.2337/diacare.18.4.517. PMID: 7497862.
[13] Brooke, John (1996). "SUS: a "quick and dirty" usability scale". In P. W. Jordan; B. Thomas; B. A. Weerdmeester; A. L. McClelland (eds.). Usability Evaluation in Industry. London: Taylor and Francis.

measure of the overall usability of the system should be reported. The SUS score ranges from 0 to 100, and is calculated as follows:

1. For items 1, 3, 5, 7, and 9, subtract 1 from the reported score
2. For items 2, 4, 6, 8, and 10, the contribution equals 5 minus the reported score
3. Sum the contributions (each will range from 0 to 4), multiply by 2.5

SUS is collected from subjects aged 12-70 years, and from caregivers of children aged 4 to <12 years at Baseline (Visit 3) as well as Visit 8 and Visit 14.

Insulin Dosing Systems: Perceptions, Ideas, Reflections, and Expectations (INSPIRE)

The INSPIRE for adults is a 22-item validated questionnaire to evaluate the impact of automated insulin dosing (AID) systems on the psychosocial functioning and quality of life (QoL) of individuals with Type 1 diabetes[14]. Each item is rated on a six-point scale, from strongly disagree (score=0) or not applicable, to strongly agree (score=4). Mean score is calculated based on answered responses, then multiplied by 25. The final score will range from 0 to 100, with higher scores indicating more positive appraisal of the AID.

INSPIRE is collected from subjects aged 8-70 years, and from caregivers of children aged 4 to <18 years at Baseline (Visit 3) as well as Visit 8 and Visit 14.

Patient Health Questionnaire-2 (PHQ-2)

The Patient Health Questionnaire-2 (PHQ-2) is a self-administered questionnaire about the frequency of depressed mood and anhedonia over the past two weeks. The PHQ-2 score is obtained by adding the score for each question (total points), with a score ranging from 0 to 6[15]. Its purpose is not to establish final diagnosis or to monitor depression severity, but rather to screen for depression. The authors identify a cut-off score of 3 as the optimal cut point for screening purposes.

PHQ-2 is collected from subjects aged 12-70 years at Baseline (Visit 3) as well as at the end of 13 weeks (Visit 9) and end of the extension period 1 (Visit 15).

7.8 OTHER DATA SUMMARIES

The distribution of each baseline characteristic or demographic parameter of interest (such as age, sex, medical history, etc.) will be presented. Data on all enrolled subjects and subjects included in mITT analysis set will be presented. Continuous variables will be summarized using count, mean, median, standard deviation, and range. Categorical variables will be summarized using counts and percentages.

[14] https://www.researchintorecovery.com/measures/inspire/
[15] Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: Validity of a Two-Item Depression Screener. Medical Care. 2003;41:1284-92.

7.9 STATISTICAL SOFTWARE

The statistical software package SAS® 9.4 or later will be used for all the data derivations, summarization, data listings and statistical analyses. Additional statistical software may be used for graphics or validation purposes as appropriate.

Certificate Of Completion

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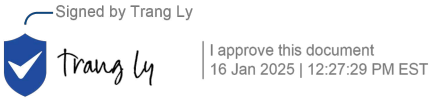
Trang Ly tly@insulet.com SVP, Medical Director Security Level: Email, Account Authentication (Required)	Signed by Trang Ly  I approve this document 16 Jan 2025 | 12:27:29 PM EST 5574B167ED01438CB4D9D3EBC2DDCFE5 Signature Adoption: Pre-selected Style Signature ID: 5574B167-ED01-438C-B4D9-D3EBC2DDCFE5 Using IP Address: 192.150.50.4 Signed using mobile With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 1/16/2025 11:47:11 AM Viewed: 1/16/2025 12:27:00 PM Signed: 1/16/2025 12:27:32 PM
Electronic Record and Signature Disclosure: Accepted: 10/17/2023 11:48:21 AM ID: 272582a3-8512-4c68-a135-92837f014fbb		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	1/16/2025 11:47:11 AM
Certified Delivered	Security Checked	1/16/2025 12:27:00 PM
Signing Complete	Security Checked	1/16/2025 12:27:32 PM
Completed	Security Checked	1/16/2025 12:27:32 PM

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

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At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. You will have the ability to download and print documents we send to you through the DocuSign system during and immediately after the signing session and, if you elect to create a DocuSign account, you may access the documents for a limited period of time (usually 30 days) after such documents are first sent to you. After such time, if you wish for us to send you paper copies of any such documents from our office to you, you will be charged a $0.00 per-page fee. You may request delivery of such paper copies from us by following the procedure described below.

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If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

Consequences of changing your mind

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. Further, you will no longer be able to use the DocuSign system to receive required notices and consents electronically from us or to sign electronically documents from us.

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Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

How to contact Fortrea Enterprise (Part 11):

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:

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To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

If you created a DocuSign account, you may update it with your new email address through your account preferences.

To request paper copies from Fortrea Enterprise (Part 11)

To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an email to and in the body of such request you must state your email address, full name, mailing address, and telephone number. We will bill you for any fees at that time, if any.

To withdraw your consent with Fortrea Enterprise (Part 11)

To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an email to jay.singleton@labcorp.com and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

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The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: https://support.docusign.com/guides/signer-guide-signing-system-requirements.

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By selecting the check-box next to 'I agree to use electronic records and signatures', you confirm that:

- You can access and read this Electronic Record and Signature Disclosure; and
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- Until or unless you notify Fortrea Enterprise (Part 11) as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by Fortrea Enterprise (Part 11) during the course of your relationship with Fortrea Enterprise (Part 11).