Cover Page

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Statistical Analysis Plan

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Approval

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List of Abbreviations and Definitions

- **AE:** Adverse event
- **BD:** Becton Dickinson and Company
- **BG:** blood glucose value
- **BGM:** Blood Glucose Meter
- **BMI:** body mass index
- **GCD:** Global Clinical Development, BD
- **GLP-1:** glucan-like peptide-1
- **CI:** Confidence Interval
- **G:** Gauge
- **HbA1c:** glycated hemoglobin
- **IFU:** Instruction for Use
- **LH:** Lipohypertrophy
- **SAE:** Serious Adverse Event
- **SAP:** Statistical Analysis Plan

- **SD:** Standard Deviation
- **TDD:** total daily dose

1 Introduction

1.1 Background and Rationale

Insulin is the drug used in the treatment of diabetes mellitus, and it is administered via injection into subcutaneous adipose tissue. Proper technique of insulin injection in diabetic patients is a prerequisite for achieving good glycemic control, a reduction in the variability of insulin absorption, and reaching optimal efficacy of the anti-diabetic drugs.

To date, several clinical trials have been conducted with the aim of evaluating the effect of proper insulin injection technique on such parameters as glycemic control, glycated hemoglobin, hypoglycemia, glycemic variability and TDD of insulin. These studies attest to the fact that the use of proper injection technique yields tangible results, namely, a reduction in percentage of glycated hemoglobin, an improved control of blood glucose level and an overall improvement of patient satisfaction with treatment. A 6-month follow-up is considered a necessary and sufficient measure for the evaluation of the above parameters. In our study, we would also like to evaluate all the above mentioned parameters with regard to proper injection technique; in addition, physicians' explanations on the injection technique will be reinforced by on-line video lessons, which will be recommended by the attending physician to patients for their own viewing.

1.2 Objectives

1.2.1 Primary Objectives

- Evaluation of the effect of personalized teaching of the optimal insulin injection technique in conjunction with the use of disposable BD Micro-Fine Plus 32G (0.23mm/32G x 4 mm) pen needles on the reduction in glycated hemoglobin (HbA1c in %) after 6 months follow up in patients with Type 1 or Type 2 diabetes .

1.2.2 Secondary Objectives

- Evaluation of the effect of optimal insulin injection technique on the total daily dose of insulin and clinical parameters of glycemic control (hypoglycemia and severe hypoglycemia requiring third party assistance).
- Evaluation of the effect of optimal insulin injection technique on glucose blood levels (measured by BGM).

1.2.3 Additional Objectives

- Evaluation of the effect of education (especially distanced learning) on patients' knowledge and their mastering insulin injection technique, including correctly alternating the injection sites, avoiding injecting the lipohypertrophy areas, and the single use of needles.

2 Study Description

This clinical trial is a prospective, post-marketing, single-arm, multiple-center clinical trial.

2.1 Study Design

A total of 90 patients will be enrolled. Each center will be offered to supply a sufficient number of patients as study subjects (up to 15 patients). Approximately half of these patients will be with lipohypertrophy (LH), and half will be without. Ideally, each center should recruit half of their patients with and half of their patients without LH. The Sponsor will monitor if the overall balance of 50%/50% is maintained and will advise study centers accordingly. The main goal is to have an equal distribution across the study, not necessarily per site, however, each study center should have at least a distribution of 1/3 versus 2/3 in each group. The optimal injection technique and choice of needle length is based on the Russian Procedural Guidelines on injection techniques and infusions used in the treatment of diabetes mellitus. These Guidelines, in turn, are based on recently published international guidelines by the Forum for Injection Technique Therapy Expert Recommendations (FITTER).

2.2 Study Population

The selection of patients will not be influenced by race, religion, socio-economic and other factors. Approximately 50% of the subjects to be enrolled will have lipohypertrophy areas and 50% of the subjects will not.

Inclusion criteria:

- Type 1 or type 2 diabetes mellitus;
- Patients (male and female) of 18 years of age and over;
- At least 1 year of experience with insulin self-administration;
- Use of insulin pen for insulin injections;
- HbA1c $>$ 7.5% measured at study entry or maximally 30 days prior to study entry;
- BMI below 40 kg/m2 at study entry;
- Daily self-control of blood glucose level;
- Access to the internet for watching video lessons;
- Only outpatients are eligible for the study;
- Availability of the patient's signed informed consent for inclusion in the study.

Exclusion criteria:

- Pregnant women or women planning to become pregnant during the time of study, breastfeeding women;
- Subjects using an insulin pump;
- Those using treatment with a GLP-1 receptor agonists alone;
- Subjects not fluent in Russian (reading and writing);
- Patients at high risk for ketoacidosis and/or hyperglycemia;
- Psychic, physical or any other reasons hampering patient participation in the study (based on the reasonable opinion of the physician-investigator).

2.3 Sample Size

Based on data observed in internal studies with similar designs, assuming an HbA1c decrease of 0.4% between baseline and 6 months and a standard deviation of paired differences of 1.2%, a sample size of 73 subjects would be needed to demonstrate statistical significance using a one sample t-test with a power

of 80% and alpha equal to 0.05. With a 20% buffer, the sample size needed is 90.

2.4 Study Procedure

The study design and calendar of events, including all the necessary visits, their order, appointment time and manipulations carried out during the visits, are presented in Figure 2.4.1.

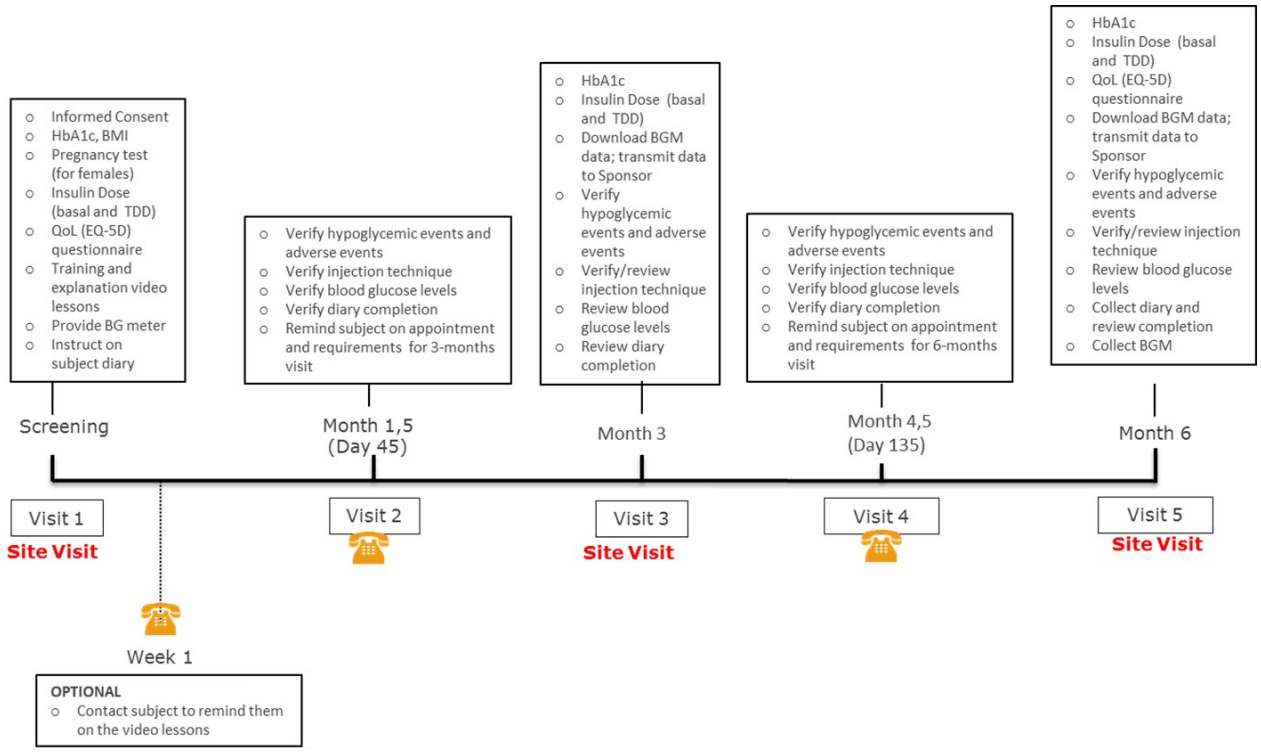

Figure 2.4.1: Study Flow

2.5 Endpoints

2.5.1 Primary Endpoints

Reduction in glycated hemoglobin (HbA1c in %) after 6 months follow up in patients with Type 1 or Type 2 diabetes.

2.5.2 Secondary Endpoints

- Change in total daily dose of insulin and clinical parameters of glycemic control (hypoglycemia and severe hypoglycemia requiring third party assistance) after 6 months follow up in patients with Type 1 or Type 2 diabetes.
- Change in glucose blood levels (measured by BGM) after 6 months follow up in patients with Type 1 or Type 2 diabetes.

2.5.3 Exploratory Endpoints

- Patients' knowledge and their mastering insulin injection technique, including correctly alternating the injection sites, avoiding injecting the lipohypertrophy areas, and the single use of needles.

- Change of lipohypertrophy, its size (length and width in mm) and localization (if applicable);
- Patients' quantitative experience with the use of distant video lessons

2.6 Acceptance Criteria

There is no acceptance criteria for this study.

3 Intended Statistical Software and Data Information

3.1 Intended Statistical Software

This document was generated with R version 4.0.2 (2020-06-22) [1] and the following packages (version) were used: assertthat (0.2.1), backports (1.2.0), base (4.0.2), BDbasics (0.3.3), broom (0.7.3), cellranger (1.1.0), cli (2.2.0), colorspace (2.0.0), compiler (4.0.2), crayon (1.3.4), datasets (4.0.2), DBI (1.1.0), dbplyr (2.0.0), dplyr (1.0.2), ellipsis (0.3.1), fansi (0.4.1), forcats (0.5.0), fs (1.5.0), generics (0.1.0), ggplot2 (3.3.2), glue (1.4.2), graphics (4.0.2), grDevices (4.0.2), grid (4.0.2), gtable (0.3.0), haven (2.3.1), hms (0.5.3), httr (1.4.2), jsonlite (1.7.2), lifecycle (0.2.0), lubridate (1.7.9.2), magrittr (2.0.1), methods (4.0.2), modelr (0.1.8), munsell (0.5.0), pillar (1.4.7), pkgconfig (2.0.3), plyr (1.8.6), purrr (0.3.4), R6 (2.5.0), Rcpp (1.0.5), readr (1.4.0), readxl (1.3.1), reprex (0.3.0), rlang (0.4.9), rstudioapi (0.13), rvest (0.3.6), scales (1.1.1), stats (4.0.2), stringi (1.5.3), stringr (1.4.0), tibble (3.0.4), tidyr (1.1.2), tidyselect (1.1.0), tidyverse (1.3.0), tools (4.0.2), utils (4.0.2), vctrs (0.3.5), withr (2.3.0), xml2 (1.3.2), xtable (1.8.4).

The study analysis will be conducted within the same environment or more recent versions.

4 Analysis Population Set(s)

- Intent-to-treat (ITT) population: All subjects who have been enrolled in this study.
- Per-Protocol (PP) population: The ITT population without any major protocol deviations. A major protocol deviation is defined as a subject not meeting the inclusion/exclusion criteria.

The primary analysis population is the ITT population. Additional analyses on the PP population may be done post-hoc per team's request.

5 Statistical Analysis/Calculations

5.1 Derived Variables

5.1.1 Total Daily Dose

Total Daily Dose will be calculated as the sum of basal and bolus insulin dose per day from both diary data and CRF. The data from the two sources will be analyzed separately.

5.1.2 Hypoglycemia

The following categories will be analyzed:

- Hypoglycemia with blood glucose $\leq$ 3.9 mmol/L is defined as a blood glucose meter reading <= 3.9 mmol/L.

- Symptomatic Hypoglycemia with blood glucose $\leq$ 3.9 mmol/L is defined as a blood glucose meter reading <= 3.9 mmol/L. and occurrence of at least 1 symptoms of low blood sugar (e.g., fast heartbeat, tiredness, sweating, extreme hunger, dizziness, tremors) reported in the diary.
- Hypoglycemia with blood glucose $\leq$ 3 mmol/L is defined as a blood glucose meter reading <= 3 mmol/L.
- Symptomatic Hypoglycemia with blood glucose $\leq$ 3 mmol/L is defined as a blood glucose meter reading <= 3 mmol/L. and occurrence of at least 1 symptoms of low blood sugar (e.g., fast heartbeat, tiredness, sweating, extreme hunger, dizziness, tremors) reported in the diary.
- Severe hypoglycemia is defined as any event requiring third party assistance.

Events that are 15 min or closer to each other will be considered to be the same event. The lowest blood glucose value from the blood glucose meter will be used to define the Hypoglycaemia category.

5.1.3 Blood Glucose

24 Hour Average Blood Glucose and other glycemic variability variables (such as MAGE, time in range, etc.) will be computed from BGM data using BD proprietary *extractGlucoseVariabilityFeatures()* and *summarizeGlycemicVariability()* functions with following arguments and associated computation per subject for different time ranges (e.g. day, study period, ...).

For BGM data, at least 10 days data for each period are needed for each time period for the analysis. The time window for baseline is defined as the first 14 days of the study. The time window for 3 month is defined as the last 14 days of the third month. The time window for end of study is defined as the last 14 days of the sixth month. The start and end of time window may be manually adjusted based on the actual visit time.

5.1.4 Quality of Life assessments (EQ-5D)

A summary score of the EQ-5D questionnaire will be calculated as in the EQ-5D-3L user guide provided by EuroQol using the proper value set.

5.2 Analysis Methods

5.2.1 Descriptive Statistics

Summary statistics will be provided for all study endpoints. For categorical data, count and percentage will be calculated and 95% confidence interval may be provided. For continuous data, mean with 95% confidence interval, standard deviation, median, and range (minimum - maximum) will be provided.

Graphical summaries may be provided:

- Boxplots showing median, 1st and 3rd quartiles or scatter plots with means and 95% confidence interval for quantitative responses.
- Barplots for discrete responses or discretized continuous responses.

5.2.2 HbA1c

For HbA1c, analysis will be performed using linear mixed effect models to evaluate the effect of personalized teaching of the optimal insulin injection technique in conjunction with the use of disposable BD Micro-Fine Plus 32G pen needles on the response. In the model, subject will be a random effect, time period (baseline, 3 months or end of study) and lipohypertrophy will be fixed effects. Two-way and three-way interactions between fixed effects will be investigated. Only significant interactions will be included in the model. Models will be used to compute estimated mean, difference between baseline and end of study, and corresponding two-sided 95% CI for responses of interest.

5.2.3 Total Daily Dose

For Total Daily Dose, analysis will be performed using linear mixed effect models to evaluate the effect of personalized teaching of the optimal insulin injection technique in conjunction with the use of disposable BD Micro-Fine Plus 32G pen needles on the response. In the model, subject will be a random effect, time period (baseline, 3 months or end of study), day in each time period, and lipohypertrophy will be fixed effects. Two-way and three-way interactions between fixed effects will be investigated. Only significant interactions will be included in the model. Models will be used to compute estimated mean, difference between baseline and end of study, and corresponding two-sided 95% CI for responses of interest.

5.2.4 Blood Glucose

For 24 Hour Average Blood Glucose, analysis will be performed using linear mixed effect models to evaluate the effect of personalized teaching of the optimal insulin injection technique in conjunction with the use of disposable BD Micro-Fine Plus 32G pen needles on the response. In the model, subject will be a random effect, time period (baseline, 3 months or end of study), day in each time period and lipohypertrophy will be fixed effects. Two-way and three-way interactions between fixed effects will be investigated. Only significant interactions will be included in the model. Models will be used to compute estimated mean, difference between baseline and end of study, and corresponding two-sided 95% CI for responses of interest.

5.2.5 Hypoglycemia

Summary statistics will be provided for the five categories of hypoglycemia events defined in Section 5.1.2. If data permits, the distribution of the hypoglycemia events during the night(12am to 6am) and during

the day (6am to 12am) will be summarized. The distribution by study month will be summarized too.

5.2.6 Injection Techniques

If data permit, a logistic mixed effect models will be used evaluate the effect of personalized teaching of the optimal insulin injection technique in conjunction with the use of disposable BD Micro-Fine Plus 32G pen needles on the percentage of subject correctly alternating injection sites. In the model, subject will be a random effect, time period (baseline, 3 months or end of study) and lipohypertrophy will be fixed effects. Two-way interactions between fixed effects will be investigated. Only significant interactions will be included in the model. Models will be used to compute estimated mean, difference between baseline and end of study, and corresponding two-sided 95% CI for responses of interest. Additional information recorded in the CRFs will be summarized.

Similar approaches will be used for percentage of subject using needles repeatedly and subject injecting into lipohypertrophy areas.

5.2.7 Change of lipohypertrophy

If data permit, a logistic mixed effect models will be used evaluate the effect of personalized teaching of the optimal insulin injection technique in conjunction with the use of disposable BD Micro-Fine Plus 32G pen needles on the percentage of subject with lipohypertrophy. In the model, subject will be a random effect, and time period (baseline, 3 months or end of study) will be fixed effects. Models will be used to compute estimated mean, difference between baseline and end of study, and corresponding two-sided 95% CI for responses of interest. Similar approaches will be used for lipohypertrophy size (length and width in mm) and localization (if applicable).

5.2.8 Patients' quantitative experience with the use of distant video lessons

Descriptive statistics will be provided for the subject who watched all video lessons or not. A post-hoc analysis may be done to compare the two groups on the clinical outcomes such as HbA1c and insulin TDD.

5.2.9 General Considerations

- Mising Insulin or Glycemic data might be imputed, as described in section 5.2.10.
- Imputation might be used during questionnaire analysis if questionnaire pre-process tools contain an imputation routine.
- p-values less than 0.05 will be considered statistically significant. Multiple comparisons adjustments will be made when adequate.
- For each model above, in case the model fails to converge for discrete responses, the random subject effect may be dropped from the model and the average difference between time periods may be calculated across all subjects.
- Initially, two-way interaction will be included into the model. However, if the interaction is not significant (p-value >= 0.05), it will be removed from the final model.
- Main effect and interaction plots may be used to graphically show significant effects for each model.
- Residual plots for each model will be drawn and reviewed to ensure there are no systematic patterns. Transformation of response and/or explanatory variables will be investigated whenever modelling assumptions are not satisfied.

- For analysis on discrete responses, a modeling approach will be attempted first and in cases where there are insufficient occurrences for model convergence or a stable model, difference in proportions between categories will be provided and non-parametric testing may be used if modeling assumptions, with or without data transformation, are not satisfied.

5.2.10 Approaches and Analyses for Missing Data and Other Data Issues

5.2.10.1 Glycaemic Data

Glycaemic data will only be included for analysis if 70% of the expected data is available, i.e. at least ten days over each 14 days period with at least on BGM measure.

Missing glycaemia data will be imputed using median value computed per period per subject when data is not available for a given day only if the data meet the availability of 70% of the expected data requirement.

5.2.10.2 Insulin Data

Insulin data will only be included for analysis if 70% of the expected data is available, i.e. at least ten days over each 14 days period with at least one basal Insulin dose record and at least ten days over each 14 days period with at least one bolus Insulin dose record. In case a patient did not use boluses, only basal requirements will have to be fulfilled. The pattern of basal and bolus doses can be different (e.g. a day with basal information can have no bolus information).

Missing basal and bolus insulin data will be imputed separately, before TDD computation, using median value computed per period per subject when data is not available for a given day only if the data meet the availability of 70% of the expected data criteria.

6 Summary of General Study Data

6.1 Subject Disposition

The number of subject enrolled, completed each visit and completed the study will be summarized.

6.2 Protocol Deviations

A list of Protocol Deviations will be provided.

6.3 Demographics and Baseline Variables

Summary Statistics will be provided for demographics and baseline variables.

6.4 Device Failure, Malfunctions and Defects

A list of Device Failure will be provided.

7 Safety Analysis

A list of AE will be provided.

8 References

[1] R Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria, 2016. URL https://www.R-project.org/.

9 Appendix

Example tables are shown below. These tables are from previous studies and just for example only.

A Tables

Table A.0.1: Population Disposition

Subject.Information	Number	Comments
Subjects Enrolled and Screened		
Subjects Randomized		
Subjects Who Completed the 45 day visit		
...		
Subjects Who Completed the Study		

Table A.0.2: Demographics (Randomized Subjects)

Characteristic		
Age		
	Mean	58.3
	Median	58.5
	SD	10.3
	Min, Max	34, 78
	Total Count	58
Gender		
	Female	31 (53.4%)
	Male	27 (46.6%)

Note: Demographics will also be provided stratified per site.

Table A.0.3: Summary Statistics for 24 Hour Average Blood Glucose (mg/dL)

Time	Characteristic	
Baseline	BG (Mean)	
Baseline	Mean	173.73
Baseline	95% Mean CI	163.51, 184.71
Baseline	Median	173.89
Baseline	SD	40.47
Baseline	Min, Max	85.13, 279.38
Baseline	Total Count	57
3 months	BG (Mean)	
3 months	Mean	173.73
3 months	95% Mean CI	163.51, 184.71
3 months	Median	173.89
3 months	SD	40.47
3 months	Min, Max	85.13, 279.38
3 months	Total Count	57
End of Study	BG (Mean)	
End of Study	Mean	178.64
End of Study	95% Mean CI	166.46, 192.89
End of Study	Median	167.83
End of Study	SD	50.37
End of Study	Min, Max	106.85, 397.94
End of Study	Total Count	57

Table A.0.4: Between-Time Point Comparisons for 24 Hour Average Blood Glucose Based on Linear Mixed Model.

Comparison	Estimate	Lwr	Upr	p.value	Result
3 months vs. Baseline	11.28	-3.11	25.67	0.122	No Sig. Diff.
End of study vs. Baseline	-2.16	-17.33	13.01	0.776	No Sig. Diff.

Table A.0.5: Summary Statistics for Number of Hypoglycemic Events

Period	Characteristic	
Baseline	Number of Hypoglycemic Events	
Baseline	0	53 (98.1%)
Baseline	1	1 (1.9%)
Baseline	Total	54
Baseline	Number of Severe Hypoglycemic Events	
Baseline	0	42 (77.8%)
Baseline	1	8 (14.8%)
Baseline	2	2 (3.7%)
Baseline	3	2 (3.7%)
Baseline	Total	54
Baseline	Incidence of Hypoglycemic Events	
Baseline	N	53 (98.1%)
Baseline	Y	1 (1.9%)
Baseline	Total	54
Baseline	Incidence of Severe Hypoglycemic Events	
Baseline	N	42 (77.8%)
Baseline	Y	12 (22.2%)
Baseline	Total	54
Baseline	Rate of Hypoglycemic Events	
Baseline	Mean	0.02
Baseline	Median	0.00
Baseline	SD	0.14
Baseline	Min, Max	0, 1
Baseline	Total Count	54
Baseline	Rate of Severe Hypoglycemic Events	
Baseline	Mean	0.33
Baseline	Median	0.00
Baseline	SD	0.73
Baseline	Min, Max	0, 3
Baseline	Total Count	54
3 months	Number of Hypoglycemic Events	
3 months	0	51 (94.4%)
3 months	1	3 (5.6%)
3 months	Total	54
3 months	Number of Severe Hypoglycemic Events	
3 months	0	42 (77.8%)
3 months	1	7 (13.0%)
3 months	2	3 (5.6%)
3 months	3	1 (1.9%)
3 months	5	1 (1.9%)
3 months	Total	54
3 months	Incidence of Hypoglycemic Events	
3 months	N	51 (94.4%)
3 months	Y	3 (5.6%)
3 months	Total	54
3 months	Incidence of Severe Hypoglycemic Events	
3 months	N	42 (77.8%)
3 months	Y	12 (22.2%)
3 months	Total	54

Table A.0.5: Summary Statistics for Number of Hypoglycemic Events continued

Period	Characteristic	
3 months	Rate of Hypoglycemic Events	
3 months	Mean	0.06
3 months	Median	0.00
3 months	SD	0.23
3 months	Min, Max	0, 1
3 months	Total Count	54
3 months	Rate of Severe Hypoglycemic Events	
3 months	Mean	0.39
3 months	Median	0.00
3 months	SD	0.92
3 months	Min, Max	0, 5
3 months	Total Count	54
End of Study	Number of Hypoglycemic Events	
End of Study	0	53 (98.1%)
End of Study	1	1 (1.9%)
End of Study	Total	54
End of Study	Number of Severe Hypoglycemic Events	
End of Study	0	44 (81.5%)
End of Study	1	7 (13.0%)
End of Study	2	2 (3.7%)
End of Study	3	1 (1.9%)
End of Study	Total	54
End of Study	Incidence of Hypoglycemic Events	
End of Study	N	53 (98.1%)
End of Study	Y	1 (1.9%)
End of Study	Total	54
End of Study	Incidence of Severe Hypoglycemic Events	
End of Study	N	44 (81.5%)
End of Study	Y	10 (18.5%)
End of Study	Total	54
End of Study	Rate of Hypoglycemic Events	
End of Study	Mean	0.02
End of Study	Median	0.00
End of Study	SD	0.14
End of Study	Min, Max	0, 1
End of Study	Total Count	54
End of Study	Rate of Severe Hypoglycemic Events	
End of Study	Mean	0.26
End of Study	Median	0.00
End of Study	SD	0.62
End of Study	Min, Max	0, 3
End of Study	Total Count	54

Table A.0.6: Summary Statistics of Number of BGM Readings

Period	Mean	95% Mean CI	Median	SD	Min, Max	Total Count
Baseline	30.32	23.79, 36.89	30.00	18.02	1, 67	28
3 months	37.12	30.38, 43.67	37.50	16.78	9, 65	24
End of Study	33.71	27.58, 39.96	34.50	15.68	6, 63	24

Table A.0.7: Between Time Point Comparisons for Incidence of Hypoglycemic Events Based on Logistic Mixed Model.

Comparison	Odds Ratio	Lwr	Upr	p.value	Result
3 months vs. Baseline	1.000	0.234	4.279	> 0.999	No Sig. Diff.
End of study vs. Baseline	0.124	0.011	1.455	0.097	No Sig. Diff.

Table A.0.8: Between Time Point Comparisons for Rate of Hypoglycemic Events Based on Negative Binomial Mixed Model.

Comparison	Ratio	Lwr	Upr	p.value	Result
3 months vs. Baseline	1.200	0.369	3.900	0.762	No Sig. Diff.
End of study vs. Baseline	0.250	0.043	1.470	0.125	No Sig. Diff.