Outpatient Reduction of Nocturnal Hypoglycemia and Hyperglycemia by Using Predictive Algorithms, Pump Suspension, and Insulin Dosing in Children and Young Adolescents (PHM3)

Statistical Analyses Plan

Version 1.1

August 15, 2017

Based on Protocol Version 6.0

Chapter 1. Objectives

The objective of the analysis is to assess the safety, feasibility, and efficacy of use of a modified algorithm that will dose insulin to minimize projected hyperglycemia (HM) overnight in addition to suspending the pump if hypoglycemia is projected (PLGS) overnight in the home environment. In particular, we will try to answer the following questions:

1. How often does a HM system dose insulin in order to prevent overnight hyperglycemia?
2. Does a PLGS+HM system minimize both hypo- and hyperglycemia when compared with PLGS-only system?
3. Does a combined predictive low- and high-glucose (PLGS+HM) system continue to prevent against overnight hypoglycemia as showed by a low-glucose suspend only (PLGS-only) system?
4. Is a PLGS+HM system safe to use in an outpatient setting?

Chapter 2. General

2.1 Study Overview

The study includes approximately 30 subjects 6 to <15 years of age with T1D and with HbA1c <10.0%. Depending on the previous CGM experience and following a CGM run-in phase, the subjects will use the study insulin and sensor at home for a minimum of 6 days/week over a 2-week period to verify that is able to use the CGM and insert the sensor, that is able to start and

stop the system appropriately, and that is able to transmit the system data to the coordinating center. This will be followed by use of the system for 42 nights in which there will be 21 nights with both high-glucose dosing and low-glucose suspension active (PLGS+HM night) and 21 nights with only low-glucose suspension active (PLGS-only night), selected through a randomization process. A night only will be counted towards the 42 night goal if there are at least 4 hours of sensor glucose data between the time the system is activated at bedtime and the time it is discontinued in the morning. The maximum number of days to complete the study will be 90 days.

Chapter 3. Included Data

3.1. Data Source

Data from the study laptop may be inaccurate or incomplete due to incorrect values entered by the subject or connectivity issues when receiving measurements. Data from device downloads may be incomplete in some situations due to device memory limitations or device damage. Therefore, blood glucose, CGM, and insulin delivery data downloaded from the respective devices will be used when available in the assessment of outcomes; data recorded from the laptop will be used as needed to fill any gaps so that the data record for a given night may reflect a combination of device download data and study laptop data.

For insulin and sensor measurements, will take all the data between system activation and system deactivation. For bedtime glucose, will take the closest blood glucose from the meter download within 30 minutes before to 5 minutes after the system activation. Record measurement as the bedtime blood glucose if such a value exists; otherwise use the bedtime blood glucose that the subject entered on the study laptop. Repeat this logic with the morning blood glucose (30min before and 5min after deactivation).

3.2. Included Nights and Subjects

Included nights/sessions

Inclusion criteria differ for subject-level vs. night level metrics (see Metrics and Analyses below for details):

- Subject-level metrics: All randomized nights (regardless of the amount of CGM data) will be included.
- Night-level metrics: Only sessions with at least 4 hours of combined download and laptop source CGM data from when the system was active until it was discontinued the following morning will be included in the night-level efficacy analysis.
- Safety analyses: For ketoses analysis, will include all records during the session and up to 2hr after the end of session. Any episodes of severe hypoglycemia, DKA, or any other serious events will be reported along with all the available details regardless when happened during the study.

Nights/sessions meeting the criteria above will be included in the analysis even if the system activation and deactivation times do not correspond to nighttime (e.g., a session starting at 8am and ending at 3pm would still be considered a "night" and would be included in the analysis).

Since the system was programmed not to suspend the pump or deliver automated correction boluses beyond 12 hours after the start of the session, all data for nights/sessions will be truncated at 12 hours. We expect to have some cases where the subject forgot to end the session in the morning and it continued running in an inert state for an extended period.

Included subjects:

- Efficacy analyses will include subjects who have a total of at least 80 available hours of CGM data from included nights (as defined above) from each treatment arm.
- Safety analyses will include all subjects regardless of availability of CGM data.

Chapter 4. Metrics and Analyses

4.1. Primary Outcome

The primary outcome for this study is the time spent in target range (70 to 180 mg/dl) as measured by the CGM. The primary analysis will follow the intention to treat principle with each night included in the treatment group assigned by randomization.

A single percentage will be calculated for each subject for each treatment arm (two values per subject) by pooling all CGM readings across randomized nights. All CGM readings will be weighted equally in the pooled percentage for each treatment arm regardless of how they distribute across nights.

Mean (SD) for the time spent in target range (70 to 180 mg/dl) will be tabulated separately by treatment arm. A repeated measures regression model with an unstructured covariance structure will be fit for the time spent in range to compare the two treatments at the patient level. The model will adjust for the mean bedtime glucose as a covariate. It is anticipated that these percentages will have a normal distribution. If residual values from the regression model have a skewed distribution then a log(x+0.005) transformation, an alternate transformation, or a nonparametric analysis based on ranks will be performed. All p-values will be two-sided.

4.2. Secondary Efficacy and Safety Metrics Analyses

Metrics listed under "Pooled subject-level CGM metrics" below will be calculated as described above for the primary outcome by combining CGM data from all nights from each subject separately for each treatment arm. These analyses will follow the intent-to-treat principle with each night analyzed according to the assigned randomization arm regardless of actual system use

- Pooled subject-level CGM metrics:
  - Mean overnight sensor glucose

- Glucose standard deviation and coefficient of variation
- Percent of sensor measurements below 50, 60, and 70 mg/dl
- Area under the curve 70 mg/dl and low blood glucose index
- Percent of sensor measurements above 180, 250, and 300 mg/dl
- Area under the curve 180 mg/dl and high blood glucose index
- Percent of sensor measurements between 70 and 140 mg/dl
- Mean morning blood glucose

Night level metrics will also be analyzed according to the assigned randomization arm. However, any nights with fewer than 4 hours of CGM data will be excluded from these analyses.

- Night-level metrics:
  - Percentage of nights with events of sensor glucose below 50, 60, and 70 mg/dl continuously for more than 0, 10, 25, 30, 60, and 120 minutes; and cumulatively for more than 30, 60, 120, and 180 minutes
  - Percentage of nights with events of sensor glucose above 180, 250, and 300 mg/dl continuously for more than 0, 30, 60, and 120 minutes; and cumulatively for more than 60, 120, and 180 minutes
  - Percent of morning with blood glucose below 50, 60, 70, between 70 and 180, and above 180, 250, and 300 mg/dl (night level data)
  - Amount of total (manual, automatic, combined) and insulin boluses

Analyses for the pooled subject-level CGM secondary outcomes will parallel that described above for the primary outcome.

For binary outcomes at the night-level (e.g., nights with at least one CGM value <60 mg/dl), a repeated measures mixed effects logistic regression to account for the correlation from the same subject (by using a spatial power structure for the nights order) and adjusting for the baseline (bedtime) sensor glucose will be fit to compare PLGS+HM vs. PLGS alone nights. Only nights with at least 4 hours of combined data will be included in these analyses.

All p-values will be two-sided.

4.3 Sensitivity Analyses

- The primary analysis will be repeated excluding nights with < 4hr of CGM data.

- The primary analysis will be repeated excluding nights when the algorithm did not:
  - trigger a pump shut-off, nor
  - trigger (PLGS+HM nights) or would have triggered (PLGS only nights) any automated insulin delivery.

- The primary analysis will be repeated excluding the first 3 hours of each night.

4.4 Additional Metrics and Analyses

4.4.1 Pump Suspension

Pump suspension is allowed during both PLGS+HM and PLGS only nights.

The total shutoff duration should be at most 180 minutes from automated pump suspension, but may be as long as 210 minutes if connectivity was lost after a suspension request, and may be even longer if the subject suspended the pump manually during the night.

The following will be tabulated:

- The number and percentage of nights with a pump suspension
- The sensor value at the first pump shut-off (PSO) for each night
- The total shutoff duration for each night.
- Among nights with PSOs, the percent of nights having at least 120 minutes suspension during any 150 minute window
- Among nights with PSOs, the percent of nights having a cumulative 180 minutes or more suspension.

4.4.2. Insulin Dosing

Automatic insulin dosing is allowed during PLGS+HM nights only.
There are subject-level insulin-on-board constraints and cumulative delivery limits.

The following will be tabulated:

- The number and percentage of nights with an automated insulin dosing among PLGS+HM nights
- The sensor value at the first dosing of the nights
- The total automated insulin will be determined for each night from the session data
- Total manual and automated + manual insulin
- Total basal insulin units
- Total basal and boluses insulin units

4.4.3. Pump Suspension and Insulin Dosing

The following will be calculated among the PLGS+HM nights from the pump download data:

- The number and percentage of nights with both a pump suspension and automated insulin dosing
- Among nights with both pump suspension and automated insulin delivery:
  - Number of pump suspensions
  - Cumulative time pump was suspended
  - Cumulative amount of automated insulin delivery

- Total insulin delivered during session (includes any manual boluses)

4.4.4 Additional metrics

- Mean and coefficient of variation (CV) sensor glucose overnight and for up to 12 hours post system deactivation.
- Percentage of sensor glucose values below 50, 60, and 70 mg/dl overnight and up to 12 hours after system deactivation.
- Percentage of sensor glucose values between 70 and 180 mg/dl overnight and up to 12 hours after system deactivation.
- Percentage of sensor glucose values above 180, 250, and 300 mg/dl overnight and up to 12 hours after system deactivation.
- Change in HbA1c from enrollment, to randomization, and to study completion visit.

Additional tabulations/figures:

- Demographics and clinical characteristics at baseline.
- Flowchart showing any dropouts prior and post randomization along with number of eligible subjects and nights by treatment arm.
- Number of subjects who did not complete the study and reasons for discontinuation.
- Number of nights per subject per treatment arm.
- Distribution of number of nights required to achieve 42 study nights.
- Among PLGS+HM nights:
  - Percentage of nights with PSO, automated insulin, both, or neither.
  - Among nights with PSO, distribution of total duration.
  - Among nights with automated insulin, distribution of total insulin including % ≥4 units overall and by time of night.
  - Among nights with sensor nadir <60 mg/dl, percent of nights with automated insulin boluses and total insulin prior to nadir.
- Among PLGS only nights:
  - Percent of nights with PSO, and those that would have had an automated insulin, both, or neither.
  - Among nights with PSO, distribution of total duration.
  - Hyperglycemia minimizer (HM) operating characteristics:
    - sensitivity defined by percentage of nights with a CGM reading ≥140 mg/dl that would have triggered an automated insulin delivery within 2 hours prior to the first such reading.
    - distribution of the timing of the automated delivery that would have occurred prior to the first CGM reading ≥140 mg/dl.
    - false positive rate defined as percent of nights with automated delivery that would have occurred with no CGM reading ≥140 mg/dl within 2 hours following the first such delivery.
- All instances of blood ketone ≥0.6 mmol/l during or immediately following a night, by treatment group.
- Percent of available CGM data during sessions by treatment group and overall.

- Percent time insulin dosing (PLGS+HM nights) and suspension components (both treatment arms) were inactive because no CGM reading was available in the prior 10 and 20 minutes.
- Percent of automated insulin boluses requested but not delivered (no bolus within the subsequent 5-minute period) for PLGS+HM nights.
- Sensor performance metrics during sessions (bias, RAD, ISO) by different reference (meter) glucose groups (cut points 70, 120, 180), treatment group, age/Tanner stage, scheduled vs. unscheduled, during vs. outside randomized nights, and overall.
- Subject-level scatterplot with % time in range by treatment arm.
- Modal overnight CGM plot with median line and IQR bands for both treatment arms from session start up to 10hr; similar plot for coefficient of variation.
- Plots with mean, CV, % in target range 70 to 180, below 70, and above 180 mg/dl CGM by treatment arm from session start up to 10hr and from session end up to 16hr.

4.8. Adverse events

Episodes of DKA and of severe hypoglycemia at any time along with any other adverse events will be printed along with any available details. Any such events will be classified as:

- During randomized phase of the trial
    - During sessions randomized to PLGS+HM
    - During sessions randomized to PLGS only
    - During day following PLGS+HM session
    - During day following PLGS only session
    - >24hr from a randomized session
- During run-in or assessment phases

The day following a randomized session will be defined as the period from when the session ends until either 16 hours later or the beginning of the next randomized session, whichever occurs first.

Statistical analyses comparing the treatment arms will be limited to events that occur during a randomized session or during the day following a randomized session as defined above. All severe hypoglycemia events will be tabulated as counts and events per 100 person-years by treatment arm. If there are enough severe hypoglycemia events, then a Poisson regression model will be fit to compare the treatment arms. The amount of follow up will be included as an offset covariate to compare the rates. Influence diagnostics will be reviewed and if outliers are present then robust Poisson regression will be used instead. Additionally, the number of subjects with at least one severe hypoglycemia event will be tabulated by treatment arm. If there are enough events, the Kaplan-Meier incidence rates will be calculated and compared between treatment groups using a log-rank test.

A similar analysis will be done for DKA events.

4.9. Additional Analyses not intended for the Primary Manuscript

- Scatterplot of sensor glucose values vs. rate of drop at the time of 1st shutoff by treatment group and overall.
- Scatterplot of sensor glucose values vs. rate of increase at the time of 1st automated bolus for PLGS+HM nights.
- Distribution of session duration by PLGS+HM and control nights.
- Percent of nights in each treatment group with at least one instance of each of the different automated monitoring alert types (Low CGM, etc.)
- Modal overnight total insulin plot (combined basal and bolus insulin) with median line and IQR bands for both treatment arms by hour of day/session.
- Subgroup exploratory analyses by subject's Tanner stage (I, II, III, or IV).
- Among PLGS+HM nights with both pump suspensions and automated insulin dosing, will calculate the time in minutes between consecutive PSOs and ABs and will tabulate it by: overall, first such event of the night, PSOs followed by ABs, and ABs followed by PSOs.
- Any changes in pump settings from the baseline visit at the 21 and 42 day follow up visits.

4.10. Additional Analyses Added After Version 1.0.

Analyses added to the pooled subject-level CGM section:

- Percent of sensor measurements below 54 mg/dl
- Area under the curve 54 mg/dl
- All these metrics will be analyzed as described above for the original subject-level metrics.

Analyses added to the night-level CGM section:

- Events for readings <54 mg/dl (similar definitions and analyses with the original ones):
  - % of nights with glucose level <54 md/dl cumulatively for a duration of >5, 60, 120, and 180min
  - % of nights with glucose level <54 md/dl consecutively for a duration of >10, 25, 30, 60, and 120min
- All these events will be analyzed as described above for the original night-level metrics.