Hybrid Closed Loop Therapy and Verapamil for Beta Cell Preservation in New Onset Type 1 Diabetes:

A Proof-of-Concept Study

Statistical Analysis Plan

Version 2.0

Corresponds to Version 5.2 of the protocol

Version History

SAP Version	Author	Approver	Effective Date	Revision Description	Study Stage	Protocol Version
1.0	Rob Henderson & Colleen Bauza	Craig Kollman	07May2020	Original Version	Enrollment has not started yet	4.1
1.1	Colleen Bauza	Craig Kollman	17 Feb2021	Added conditions to calculate c-peptide;corrected typos	Enrollment ongoing	4.4
1.2	Colleen Bauza	Craig Kollman	20 April 2021	Added condition to HCL per-protocol analysis	Enrollment ongoing	4.4
1.3	Ryan Bailey	Craig Kollman	14 July 2022	Revised methods for handling skewed outcomes	Enrollment completed. Follow-up ongoing	5.2
2.0	Ryan Bailey	Craig Kollman	27 September 2022	Included type of device as a fixed effect in models comparing CGM metrics between verapamil and placebo groups. Added more subgroup analyses. Replaced hospitalizations with SAEs as a safety metric.	Enrollment completed. Follow-up ongoing	5.2

Author: Ryan Bailey
I am digitally signing this document
2022-09-27 14:14-04:00

Senior Statistician: Craig Kollman
I am digitally signing this document
2022-09-27 14:45-04:00

JCHR Project Director: Colleen Bauza
I am digitally signing this document
2022-09-28 15:38-04:00

Protocol Co-Chair Gregory P. Forlenza Digitally signed by Gregory P. Forlenza Date: 2022.09.28 16:09:35 -06'00'

Protocol Co-Chair Antoinette Moore 30 Sept 2022

1. Study Overview

The purposes of this study are to

1) to determine if initiation of HCL therapy plus intensive diabetes management soon after diagnosis of stage 3 T1D can achieve near-normalization of glucose concentrations that preserves beta cell function (Cohort A and Cohort B will be combined for the analysis)
2) to determine if oral verapamil started soon after diagnosis of stage 3 T1D preserves beta cell function (Cohort A)

There are two cohorts in this trial

A) body weight ≥30 kg
B) body weight <30 kg

Randomization schedules will be separate for Cohort A and Cohort B and will be stratified by site. Cohort A will be participating in a factorial design arm. Eligible participants will be randomly assigned (1:1:1:1) to one of 4 groups:

- HCL and placebo
- HCL and verapamil
- non-HCL and placebo
- non-HCL and verapamil.

Cohort B will be not be assigned to verapamil due to their lower body weight. These participants will be randomly assigned 2:1 to either HCL or non-HCL.

Participants assigned to HCL will receive intensive diabetes management with frequent contacts by study staff with the goal of near-normalization of glucose concentrations. Participants assigned to non-HCL will receive a Dexcom G6 CGM and diabetes management will follow usual care.

Participants will be followed for 12 months from diagnosis, with visits timed from diagnosis at 6, 13, 26, 39, and 52 weeks. Participants will have a mixed meal tolerance test (MMTT) performed, HbA1c measured, insulin dose (units/kg/day) recorded, CGM data uploaded, and pregnancy testing performed (if indicated) at some or all of the previously noted timepoints.

<u>Additional Procedures for Cohort A</u>

Drug will be double blinded. Cohort A will have additional safety visits 1 week after initiation of study drug and after each study drug dose increase.

2. Consistency of Statistical Analysis Plan with Protocol

Prior to the start of the study, the following secondary outcomes have been added that were not specified in the protocol:

- Percentage of participants with peak C-peptide ≥ 0.2 pmol/ml
- Percentage of time sensor glucose from 70 to 140 mg/dL
- Percentage of participants with ≥70% of sensor glucose values from 70 to 180 mg/dL
- Percentage of time sensor glucose > 140 mg/dL
- Total daily insulin per kg
- Basal: Bolus ratio

Serious adverse events has been added as a safety outcome in place of hospitalizations.

Otherwise, the author of this SAP has verified that the analyses described in this document are consistent with the version of the protocol listed in the version history table above.

3. Primary Statistical Hypotheses

The primary outcome is the C-peptide area under the curve (AUC) in response to a 2-hour MMTT at 52 weeks.

3.1 HCL vs. non-HCL

- *Null Hypothesis:* There is no difference in the C-peptide AUC in response to a 2-hour MMTT at 52 weeks between HCL with intensive care and non-HCL with standard care for the combined Cohort A and B population.
- *Alternative Hypothesis:* There is a nonzero difference in the C-peptide AUC in response to a 2-hour MMTT at 52 weeks between HCL with intensive care and non-HCL with standard care for the combined Cohort A and Cohort B population.

3.2 Verapamil vs. Placebo

- *Null Hypothesis:* There is no difference in the C-peptide AUC in response to a 2-hour MMTT at 52 weeks between verapamil and placebo for the Cohort A population.
- *Alternative Hypothesis:* There is a nonzero difference in the C-peptide AUC in response to a 2-hour MMTT at 52 weeks between verapamil and placebo for the Cohort A population.

4. Sample size

The sample size calculation is detailed in a separate document and is summarized below. Sample size was driven by the verapamil vs. placebo comparison as the test only includes participants in Cohort A. The mean of the transformed C-peptide (log(AUC + 1)) and the root mean square error in the placebo group were assumed to be 0.315 and 0.18, respectively, based on 90% CIs from prior studies (1). The corresponding geometric-like mean C-peptide value of 0.370 pmol/mL was calculated using the inverse transformation: exp(0.315) − 1. A recent randomized trial (2) found a 62% increase in mean C-peptide in verapamil compared with placebo, although

the total sample size was small (N=24) and confidence intervals were wide. Therefore, this study assumed a smaller, 50% increase in mean C-peptide using verapamil. The expected geometric-like mean C-peptide value in the verapamil arm was $0.370 \cdot 1.50 = 0.555$ pmol/mL. After a log(x+1) transformation, the mean values in the control and treatment groups are 0.315 and 0.441, respectively, giving a treatment effect of 0.441-0.315=0.126.

With these estimates, a sample size of 88 participants in Cohort A was calculated to provide 90% power with a 5% two-sided type 1 error rate and a 1:1 treatment group allocation to detect a verapamil vs. placebo treatment group difference assuming the true relative difference between groups was 50%. To account for a 10% dropout rate, the sample size in Cohort A will be 98 participants.

A sample size of 33 participants for Cohort B was selected based on convenience. Participants in Cohort B will be allocated to either HCL or non-HCL in a 2:1 treatment group allocation. Thus, 131 participants are expected tobe enrolled in either Cohort A or Cohort B with approximately 71 participants in HCL/intensive care and 60 participants in non-HCL/standard care arm. Assuming around a 10% dropout rate, an HCL/intensive care treatment effect of 50%, and an upper confidence limit estimate of 0.18 for the standard deviation (same presumed estimates for verapamil vs. placebo comparison), this study has 96% power to detect a significant HCL/intensive care vs. non-HCL/standard care treatment group difference with a type 1 error rate of 5%.

5. Outcome Measures

Primary Efficacy Outcome

The primary outcome is the C-peptide in response to a 2-hour MMTT at 52 weeks. This is measured as the area under the stimulated C-peptide curve (AUC).

Secondary Efficacy Outcomes

C-peptide

- C-peptide AUC at 13, 26, and 39 weeks (52 weeks is primary outcome)
- Peak C-peptide during a 2-hour MMTT at 13, 26, 39, and 52 weeks
- Percentage of patients with peak C-peptide $\geq$ 0.2 pmol/ml at 13, 26, 39, and 52 weeks

CGM Metrics

The following CGM-derived indices will be computed over the study period for 24 hours, daytime (6:00am to 11:59pm) and nighttime (midnight to 5:59am) at 6, 13, 26, 39, and 52 weeks:

- Mean glucose
- Percentage of time sensor glucose from 70 to 180 mg/dL
- Percentage of time sensor glucose from 70 to 140 mg/dL
- Percentage of patients with $\geq$70% of sensor glucose values from 70 to 180 mg/dL
- Percentage of time sensor glucose >140 mg/dL
- Percentage of time sensor glucose >180 and >250 mg/dL

- Percentage of time sensor glucose <54 and <70 mg/dL
- Coefficient of variation

HbA1c

Values at 13, 26, 39, and 52 weeks will include the following:

- Mean HbA1c
- Percentage of patients with an HbA1c <7.0% and <6.5%

Insulin

Values at 6, 13, 26, 39, and 52 weeks

- Total daily insulin per kg
- Basal: Bolus ratio

5.1 C-Peptide

Area Under the Curve (AUC)

The stimulated C-peptide AUC will be calculated for an MMTT if the following conditions hold:

- A C-peptide measurement available at 0 minutes.
- At least three C-peptide measurements available among the following 5 times: 15 minutes, 30 minutes, 60 minutes, 90 minutes, and 120 minutes.
- At least one C-peptide measurement available at 90 minutes or 120 minutes.
- No two consecutive C-peptide measurements missing.

If any of these conditions is violated, the C-peptide AUC will be treated as a missing value for that visit. If it is discovered that the MMTT was completed while the participant was in closed loop or while the participant was not fasting, those MMTT results will also be treated as missing for that visit.

If the lab deems the C-peptide AUC value to be below the lower limit of detection (LLOD), the C-peptide value will be assigned the value of ½ of the LLOD, akin to TrialNet (3).

For each MMTT, the starting time of the MMTT will be defined as t=0 if the C-peptide value is available at that time point.

The trapezoidal rule will be used to calculate the stimulated C-peptide AUC as a weighted sum of the C-peptide measurements. Throughout the calculation, target times for C-peptide measurements will be used (as opposed to the actual measurement times).

If the C-peptide measurement at 120 minutes is not available, the following steps will be used to calculate AUC:

- Calculate AUC_{90} from C-peptide measurements taken between baseline and 90 minutes
- Calculate AUC as $AUC_{90} \times (120/90)$

Peak

This will be defined as the maximum of all C-peptide values during the MMTT, which can occur at t=0. The rules for handling any missing measurements during the MMTT will be the same as listed above for the AUC. Thus, peak C-peptide will be missing for a visit if and only if C-peptide AUC is also missing.

5.2 CGM Metrics

Note that no pre-randomization CGM data are collected in this protocol (new onset patients) so no baseline CGM metrics will be calculated.

Participants assigned to a non-HCL group will be provided a commercially available Dexcom G6 CGM. Participants who stop using a CGM or have insufficient CGM data will wear a blinded Dexcom G6 for approximately 10 days at 6, 13, 26, 39 and 52 weeks. The CGM indices listed above will be computed separately at each follow-up visit including all unblinded data 28 days prior to the visit date and any data from a blinded sensor placed at the visit (or prior to the visit at 52 weeks). A minimum of 5 days (120 hours) of CGM data will be required to calculate CGM indices at each visit.

For daytime (6:00am to 11:59pm) versions of the CGM metrics, at least 80 hours of data will be required; and for the nighttime versions (midnight to 5:59am), at least 40 hours of data will be required.

6. Primary Analyses

Primary analyses will follow the intent to treat principle. Primary outcome is C-peptide AUC at the 52-week visit. The protocol window is 52-weeks from diagnosis ± 14 days, but out-of-window MMTT results will be included in the analysis if obtained within 52 weeks from diagnosis ± 42 days (Day 322-406 from the date of diagnosis). Any MMTT results outside this analysis window will be excluded from the primary analysis and treated as missing data.

6.1 HCL vs. non-HCL

The HCL/intensive care versus non-HCL/standard care comparison will combine participants from Cohort A and B. Comparisons for HCL versus non-HCL will be pooled over verapamil groups (verapamil, placebo, neither [Cohort B]). Summary statistics appropriate to the distribution, mean (SD) or median (quartiles) of log(AUC+1), will be tabulated for each treatment group at 52 weeks. Boxplots, with HCL vs Non-HCL groups next to each other, will be produced for each visit.

A constrained longitudinal regression model will be constructed with log(AUC+1) as the dependent variable controlling for age, time from diagnosis to randomization, verapamil group (verapamil, placebo, or neither [Cohort B]), and clinical site (random effect). C-peptide values at baseline, 13, 26, 39 and 52 weeks will be included in the longitudinal model which will account for the correlated data from the same participant using an unstructured covariance matrix. If there are convergence issues, a simpler covariance structure (e.g., autoregressive or compound

symmetry structure) will be used. The model specified above is equivalent to adjusting for baseline as a covariate, but also has the advantage of being able to handle any cases of missing baseline.

A time by treatment (HCL) interaction will be included in the model so that different treatment effects can be estimated. The treatment effect at 52 weeks from this model (point estimate, 95% confidence interval (CI), and p-value) will be reported as the primary analysis results.

The log(AUC+1) transform is expected to make the residuals normally distributed, but regression diagnostics will be performed to check the residuals. If the residuals have a skewed distribution then robust regression using M-estimation will be used.

Missing data will be handled by the method of direct likelihood.

6.2 Verapamil vs. Placebo

The verapamil vs. placebo comparison will only include participants in Cohort A and will be pooled over the HCL and usual care groups.

Summary statistics appropriate to the distribution, mean (SD) or median (quartiles) of log(AUC+1), will be tabulated for verapamil versus placebo at 52 weeks.

A similar constrained longitudinal analysis will be performed controlling for HCL or no HCL as a covariate.

7. Analysis Cohorts

7.1 Intent to Treat

The primary analyses will follow the intention-to-treat principle. They will include all randomized participants, and data will be analyzed based on the treatment assigned from randomization regardless of the actual treatment received. Unless specified, all analyses will be ITT. As noted above, any data from an MMTT where it is known that the participant was in closed loop at the time or the participant was not fasting will be excluded from analysis.

7.2 Per Protocol Analyses

In addition to ITT, per-protocol analyses for the primary outcome will be conducted for the HCL/intensive therapy group vs. non-HCL/standard care comparison and, separately, for the verapamil vs. placebo comparison. The per-protocol analysis will be limited to those with non-missing 52-week visit data.

The per-protocol analysis for HCL/intensive therapy vs. non-HCL/standard therapy will include HCL participants who use the HCL system at least 85% of the time over the course of the study and all non-HCL participants. If it is discovered that a non-HCL participant was using closed loop during the study, his/her data will be excluded from this per-protocol analysis.

The per-protocol analysis for verapamil vs. placebo will only include participants in Cohort A who have taken at least 80% of the study drug (both active and placebo groups) over the course of the study.

For each analysis noted above, the per-protocol analysis will not be conducted if the N for the analysis is $\geq$ 95% of the N in the primary intent-to-treat analysis.

8. Secondary Analyses

As described above for the primary analysis, comparisons of HCL versus non-HCL will include cohorts A and B and will be pooled over verapamil groups. Comparisons of verapamil versus placebo will be limited to Cohort A and will be pooled over HCL and usual care groups.

Descriptive summary statistics appropriate to the distribution will be given for each secondary efficacy outcome listed above in Section 5 by treatment group at each visit. Corresponding boxplot figures of baseline and 52 weeks, boxplot figures over time, scatterplots of baseline versus 52 weeks, and histograms of baseline, 26 weeks, and 52 weeks will be constructed for selected metrics.

8.1 Formal Statistical Comparisons of Treatment Groups

C-peptide Related Secondary Efficacy Outcome

Formal statistical comparisons of treatment groups will limited to C-peptide AUC at 13, 26, and 39 weeks (52 weeks is the primary analysis described above).

Other Secondary Efficacy Outcomes

Formal statistical comparisons of treatment groups for other secondary efficacy outcomes will be limited to the following at 26 and 52 weeks:

- Mean HbA1c
- Total daily insulin per kg
- Selected overall (24 hours) CGM indices:
  - Mean glucose
  - Percentage of time sensor glucose from 70 to 140 mg/dL
  - Percentage of time sensor glucose from 70 to 180 mg/dL
  - Percentage of time sensor glucose >180 mg/dL
  - Percentage of time sensor glucose >250 mg/dL
  - Percentage of time sensor glucose <54 mg/dL
  - Percentage of time sensor glucose <70 mg/dL

Separate comparisons for HCL versus non-HCL and verapamil versus placebo will be done similarly as described above for the primary analysis. Except where noted otherwise below in Sections 8.3 and 8.5, the general approach for analysis of secondary outcomes will be as follows: For each outcome, a constrained longitudinal model will be fit adjusting for age, time from diagnosis to randomization, verapamil group (for HCL analysis), HCL group (for verapamil

analysis) and clinical site as a random effect. A treatment by time interaction will be included in the model and treatment effects (and 95% CI) will be reported separately at 26 and 52 weeks. Regression diagnostics and remedy for a non-normal distribution will be as described above for the primary analysis. Missing data will be handled by the method of direct likelihood.

8.2 Included Data

The following analysis windows will be applied to determine which data values collected at a follow-up visit will be included in the analysis. The windows indicated in the protocol are expanded here so that data collected at some out of window visits may still be included. If there are multiple visits with non-missing data values in the same analysis window, the one closest to the target date (center of window) will be used for analysis.

These windows apply to C-peptide, HbA1c, and insulin. These do not apply to the CGM metrics (see Section 5.2).

Visit	Protocol Target Window Range [a]	Protocol Allowable Window Range [a]	Proposed Analysis Window [a]
Week 13 (3 mo)[b]	91 ± 3 days	91 ± 7 days	91 ± 28 days
Week 26 (6 mo)[b]	182 ± 7 days	182 ± 14 days	182 ± 28 days
Week 39 (9 mo)[b]	273 ± 7 days	273 ± 14 days	273 ± 28 days
Week 52 (12 mo)[b]	364 ± 7 days	364 ± 14 days	364 ± 42 days

a - Days from diagnosis.
b - Applies to C-peptide (AUC and peak), HbA1c, and insulin.

8.3 C-peptide Values

The same log(x+1) transformation mentioned above for AUC values in the primary analysis will be used for both AUC and peak at all time points. Note that TrialNet refers to the back-transform of the mean of the log(x+1) values as the "geometric-like" mean. Treatment group comparisons of C-peptide AUC at 13, 26, and 39 weeks will be taken from the same longitudinal model described above for the primary analysis.

8.4 HbA1c

Analyses will utilize values from the central laboratory. Local HbA1c values will not be utilized.

8.5 CGM Metrics

The descriptive analyses described above will be done for each CGM index listed in Section 5, separately for:

- Overall CGM data (24 hours per day)
- Daytime (limited to CGM readings from 6:00 am – 11:59 pm)
- Nighttime (limited to CGM readings from midnight – 5:59 am).

Boxplots and scatterplots will be limited to selected CGM metrics at each of the 3 times of the day listed above.

Formal statistical comparisons of treatment groups will be done for the selected CGM indices listed above and will be limited to the 24 hour versions (analysis of daytime and nighttime versions will be descriptive only). Analysis will follow the method described above with three exceptions:

- The longitudinal model will not be constrained because no baseline values will be available.
- The unconstrained longitudinal model will include 6 week values.
- For verapamil vs. placebo comparisons the type of CGM sensor used (Medtronic, Dexcom) will be included as a covariate in the models. This covariate will be allowed to differ within subject if the participant changes devices between visits. If the participant switches sensors in the 28 day period used to calculate CGM metrics, data from both sensors will be used to calculate metrics and the value for the sensor covariate will be set equal to the sensor which contributed the most data.

It is likely that percentage of sensor values below 54 mg/dL and possible that the percentage of sensor values above 250 mg/dL will have a skewed distribution. The other CGM metrics are anticipated to have an approximate normal distribution. As described above for the primary analysis, robust regression with M-estimation will be used to analyze skewed outcomes.

The percentage of patients with ≥70% of sensor values from 70 to 140 mg/dL will be analyzed using generalized estimating equations (GEE) logistic regressions adjusting for baseline HbA1c, age, time from diagnosis to randomization. Clinical site will be treated as a repeated factor using a compound symmetry covariance structure. A risk-adjusted difference and 95% confidence interval for the percentages will be calculated using the method of Kleinman and Norton (4). This analysis will be available cases only. There will be no imputation of missing data.

9. Interaction Analyses

A factorial design is being used for this study because it is believed to be unlikely that the device (HCL) and drug (verapamil) would interact with each other. An interaction test will be conducted to explore this assumption. This analysis will be limited to cohort A. Note that this study has not been powered to detect interaction. Thus, this analysis is considered exploratory and no primary conclusions about the efficacy of either HCL or verapamil will be based solely on the results of this analysis. If the interaction term is significant, separate results also will be reported (described below).

In cohort A, the same constrained longitudinal analysis model described above for the primary analysis of C-peptide AUC at 52 weeks (Section 7.2) will be fit with the addition of a device by drug interaction. If there is evidence for an interaction at 52 weeks ($p<0.05$), the following additional analyses will be performed:

- Baseline Characteristics

  A separate table for Cohort A, one column for each of the 4 combinations of HCL and Verapamil.

- HCL vs. non-HCL

Summary statistics for C-peptide AUC at 52 weeks will be given separately for each of the 4 treatment group combinations. Boxplots will be given for baseline, 6, 13, 26, 39 and 52 weeks with one box for each of the 4 treatment combinations at each visit. The point estimate, 95% confidence interval and p-value at 52 weeks will be given from the model described above for the HCL effect separately in the verapamil and placebo groups. The HCL effect will also be estimated separately in cohort B.

- Verapamil vs. Placebo

  Analogous analyses will be performed as described in the previous bullet reversing the roles of HCL and verapamil (Cohort A only).

10. Sensitivity Analyses

10.1 Confounding

Imbalances between groups in important covariates are not expected to be of sufficient magnitude to produce confounding. The primary analysis described above in Section 7 includes a fixed, pre-specified list of covariates. As an additional sensitivity analysis, any baseline demographic or clinical characteristics (see Section 14 below) observed to be imbalanced between HCL or verapamil treatment groups will be added as covariates in the primary analyses. The determination of a meaningful balance will be based on clinical judgement and not a p-value. This assessment of baseline differences will be made blinded to the outcome data.

10.2 Missing Data

It is worth emphasizing that any statistical method for handling missing data makes a number of untestable assumptions. The goal will be to minimize the amount of missing data in this study so that results and conclusions will not be sensitive to which statistical method is used.

To that end, a number of methods will be handle any missing data. As noted above in Section 7, the primary analysis will use the method of direct likelihood. Additional sensitivity analyses will handle missing data by:

- Rubin's multiple imputation
- Multiple imputation with a pattern mixture model
- Available cases only

11. Subgroup Analyses

Subgroup analyses will be conducted separately for the two primary analyses (HCL and verapamil). Interpretation of the analyses will be made with caution and tests only performed if the overall treatment effect from the corresponding primary hypothesis is significant ($P<0.05$). The general approach for these exploratory analyses will be to add an interaction term for the subgroup factor by treatment into the model used for the primary analyses. A similar analysis will be repeated for time in range 70-180 mg/dL. The following baseline factors will be tested:

- Age (<12, ≥ 12 years old)

- Sex
- Tanner staging (I vs II-V)
- Time since diagnosis at randomization
- Presence of DKA at diagnosis at randomization
- HbA1c at randomization
- C-Peptide AUC at randomization
- Antibody levels at screening
- Pre-existing autoimmune diseases

The p-value for any categorical variable will only be calculated if there are a minimum of 10 subjects per treatment group.

12. Additional Exploratory Analyses

12.1 C-peptide

The following tabulations will be performed at 13, 26, 39, and 52 weeks by treatment group:

- Peak C-peptide during a 2-hour MMTT
- Percentage of patients with peak C-peptide $\geq$ 0.2 pmol/ml

12.2 HbA1c

The percent of participants with HbA1c < 6.5% and percent < 7.0% will be tabulated at 13, 26, 39, and 52 weeks by treatment group.

12.3 CGM Metrics

For daytime and nighttime, each CGM metric listed in Section 5 will be tabulated accordingly at 6, 13, 26, 39, and 52 weeks by treatment group.

12.4 Insulin

The following tabulations will be performed at 6, 13, 26, 39, and 52 weeks by treatment group:

- Total daily insulin dose per kg
- Basal:Bolus ratio

12.5 C-peptide and Glycemic Control

To evaluate the relationship between C-peptide and glycemic control, scatterplots will be created at each time of the following factors on the horizontal axis, with C-peptide AUC on the vertical axis:

- CGM-measured % in range 70-180 mg/dL

- CGM-measured % above 180 mg/dL
- CGM-measured % below 70 mg/dL
- CGM-measured % below 54 mg/dL
- Glucose CV
- Mean HbA1c
- HbA1c CV
- Insulin dose adjusted percent time in range (70-180 mg/dL)

A longitudinal regression model will be fit with C-peptide as the dependent variable and time in range as the predictor variable separately for the HCL and non-HCL arms pooled over verapamil arms. Curves will be constructed for HCL and non-CL analogous to the DCCT analysis of HbA1c and retinopathy [5]. Similar curves will be constructed for verapamil and placebo arms and all four combinations if interaction is detected (see Section 9 above).

Similar to the model described above, a longitudinal regression model will be used to compare C-peptide between those who achieved high (> 85%) vs lower (< 65%) time in range separately for the HCL and non-HCL arms pooled over verapamil arms. The cutoffs for the high and low time in range groups may be adjusted after reviewing the distribution.

Additional exploratory analyses will be done using the other CGM metrics (and HbA1c) listed above and various combinations thereof. Model selection techniques with shrinkage (e.g., LASSO) will be used to determine the combination of CGM metrics that best predict C-peptide, potentially adjusting for confounding factors such as age and sex. Since these are exploratory analyses, the statistical methods used may be data-driven depending on results observed from initial analyses.

13. Safety Analyses

All reported adverse events will be sorted by date and listed.

For SH events, DKA events, and serious adverse events (excluding DKA and SH events), appropriate summary statistics for the following outcomes will be tabulated by treatment group.:

- Number of events per participant
- Number of participants with at least one event
- Incidence rate per 100 person-years

As described above for the efficacy analyses, safety comparisons of HCL versus non-HCL will combine cohorts A and B, and comparisons of verapamil versus placebo will be restricted to cohort A. Formal statistical comparisons will only be performed if at least 5 events occur during the study. The proportion of participants with at least one event will be compared using generalized estimating equations (GEE) logistic regression adjusting for age, and time from diagnosis to randomization. Clinical site will be treated as a repeated factor using a compound symmetry covariance structure. A risk-adjusted difference and 95% confidence interval for the

percentages will be calculated using the method of Kleinman and Norton (4). If the model does not converge then Barnard's test will be used instead. Incidence rates will be compared using a Poisson regression model adjusting for age and time from diagnosis to randomization as fixed effects and clinical site as a random effect. Models for DKA outcomes will also include presence or absence of DKA at diagnosis as a covariate.

For SH events, separate analyses also will be done for the outcomes listed above that will only include events that resulted in seizure or a loss of consciousness (if there are at least 5 such events).

For the verapamil vs. placebo comparison the frequency of adverse events stratified by MeDRA class will be reported.

14. Protocol Adherence and Retention

Tabulations and figures by treatment group to assess protocol adherence will include:

- Flowchart accounting for all subjects according to treatment group for all visits
- Visit completion rates for each follow up visit
- Protocol deviations
- Numbers and reasons for unscheduled visits and phone calls

HCL system use, verapamil, and placebo adherence will be tabulated at each time point and reported in a table.

15. Baseline Descriptive Statistics

Baseline demographic, outcome, and covariate characteristics will be summarized with counts (percentages), mean (SD), median (quartiles) as appropriate to the distribution. There will be two tables, one for HCL vs. non-HCL in the combined A+B cohort, and another for verapamil vs. Placebo, including only cohort A. For each of these tables, there will be a total column.

- Age
- Gender
- Race
- Ethnicity
- Annual Household income
- Education
- Health Insurance
- DKA at diagnosis
- HbA1c lab
- C-peptide AUC
- Time since diagnosis at randomization
- Tanner Staging (I vs II-V)

- Blood pressure (systolic/diastolic)
- BMI

16. Device Issues

All reportable device issues occurring during the study will be tabulated and reported in a table.

17. Planned Interim Analyses

No formal interim analyses or stopping guidelines are planned for this study.

The DSMB will review data for safety per the DSMB Standard Operating Procedures approximately every six months. The data to be reviewed will include information regarding adverse events, device issues, and protocol adherence/deviations as they may relate to participant safety.

18. Multiple Comparisons

For the primary analyses, no adjustments for multiplicity will be made because two different interventions are being tested separately.

For secondary analyses the false discovery rate (FDR) will be controlled using the adaptive Benjamini-Hochberg procedure separately for the HCL and verapamil analyses. For these analyses, the adjusted p-value and 95% confidence interval will be reported.

There will be no adjustments for multiple comparisons on safety analyses, sensitivity analyses, or per protocol analyses.

18. References

1. Lachin JM, McGee PL, Greenbaum CJ, et al. Sample size requirements for studies of treatment effects on beta-cell function in newly diagnosed type 1 diabetes. *PLoS One.* 2011;6(11):e26471.

2. Ovalle F, Grimes T, Xu G, et al. Verapamil and beta cell function in adults with recent-onset type 1 diabetes. *Nature medicine.* 2018;24(8):1108-1112.

3. Greenbaum CJ, Beam CA, Boulware D, et al. Fall in C-Peptide during first 2 years from diagnosis: evidence of at least two distinct phases from composite type 1 diabetes TrialNet data. *Diabetes* 2012; 61(8): 2066-2073.

4. Kleinman LC, Norton EC. What's the risk? A simple approach for estimating adjusted risk measures from nonlinear models with logistic regression. *Health Services Research* 2009; 44(1): 2009 Feb.

5. Diabetes Control and Complications Trial Research Group: The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the Diabetes Control and Complications Trial. Diabetes, 1995; 44:968-983.