The Pediatric Artificial Pancreas Automated Initialization trial (PEDAP-AI): A Pilot Study of AI Advisor-Driven Pump Initiation and Parameter Adaptation in Young Children with Type 1 Diabetes

Statistical Analysis Plan

Version 2.0

Corresponds to Version 5.0 of the Protocol

Version History

SAP Version	Author	Approver	Effective Date	Revision Description	Study Stage	Protocol Version
1.0	Zachariah Reed	Craig Kollman	September 8, 2023	Initial	Pre-Enrollment	4.0
2.0	Zachariah Reed	Craig Kollman	May 10, 2024	Updated to accommodate protocol changes regarding enrollment of pump users; corrected definition of CGM-measured hypoglycemic events	In progress	5.0

Author: Zachariah Reed
I agree to the terms defined by the placement of my signature in this document
2024-05-10 09:34-04:00

Senior Statistician (JCHR Director of Biostatistics): Craig Kollman
I am electronically signing this document
2024-05-10 09:55-04:00

JCHR Project Director: John Lum
I agree to the terms defined by the placement of my signature in this document
2024-05-10 11:28-04:00

Sponsor: Marc D Breton 18
2024.05.10 09:28:57 -04'00'

TABLE OF CONTENTS

I Study Overview

This document outlines the statistical analyses to be performed for the PEDAP-AI study. The following table provides an overview.

Table **I.** Study Ove,n iew

PARTICIPANT AREA	DESCRIPTION
Ti tle	The Pediatric Artificial Pancreas Automated Initialization trial (PEDAP-AI): A Pilot Study of Al Advisor-Driven Pump Initiation and Parameter Adaptation in Young Children wi1h Type I Diabetes
Pfecis	**A** single-arm pilot study of Al Advisor-drive nat-home closed loop system initiation and parameter adaptation in you1hage 2 to <6 years old.
lnn ·stigational De,i c.e	Tandem t:slim X2 wi1h Control-IQ and !:connect mobile application and Dexcom G6 or G7 system, connected to WA cloud-based Physician Dashboard
Objectins	The objective of the study is to obtain safety data and exploratory glycemic control data wi1h initiation and use of **a** closed loop control (CLC) system (t:slim X2 with Control-IQ Technology) in young children with initial selection of pump parameters and subsequent periodic parameter adjustment driven by an Al-based Advisor system over **a** 8-week period.
Study Design	In this single-arm intervention trial, all participants will use the study system (pump and CGM) in closed-loop mode for 8 weeks.
Nnmber of *Sites*	-3 US clinical centers
End points	The key safety outcomes are adverse events related to hypoglycemia and hyperglycemia, CGM-measured time spent below 54 mg/dL, and CGM-measured time spent above 250 mg/dL. CGM-measured endpoints will be tested against baseline for non-inferiority **Efficacv** Glycemic outcomes including time in target range 70-180 mg/dL (TIR) and various other CGM measures of hypo- and hyperglycemia will be assessed and tested for superiority against baseline and a matched historical control population from the prior PEDAP study that did not involve the use of any Al-driven pump parameters.
Population	**Ke.v Inclusion C1i.te-ria** 1. Clinical diagnosis, based on investigator assessment, of type I diabetes for at least I **month** 2. Familiarity and use of **a** carbohydrate ratio for meal boluses 3. Age;;:2 and <6 years old 4. Using a Dexcom CGM at the time of enrollment, with use on at least 21 out of the prior 28 days 5. Living with one or more parent/legal guardian knowledgeable about emergency procedures for severe hypoglycemia and able to contact emergency services and study staff. 6. Parent/guardian has a phone that can run the Tandem !:connect Mobile App (typically Android 10 or above or iOS 15 or above) 7. Willingness to use the !:connect Mobile App as needed during the study and ensure connectivity for a data upload at least once per day 8. Investigator has confidence that the parent can successfully operate all study devices and is capable of adhering to the protocol 9. Willingness to switch to lispro (Humalog) or aspart (Novolog) if not using already, and to use no other insulin besides Jisp ro (Humalog) or aspart (Novolog) during the study for participants using a study-provided Tandem pump during the study. 10. Total daily insulin dose (TDD) at least 5 U/day I I. Body weight at least 20 lbs 12. \Willinoness not to start anv new non-insulin ducose-lowerine: aizent durine: the course

PARTICIPANT AREA	DESCRIPTION
	of the trial 13. Participant and parent(s)/guardian(s) willingness to participate in all training sessions as directed by study staff 14. Parent/guardian proficient in reading and writing English 15. Live in the United States, with no plans to move outside the United States during the study period **Key Exclusion Criteria** I. Concurrent use of any non-insulin glucose-lowering agent (including GLP-1 agonists, Symlin, DPP-4 inhibitors, SGLT-2 inhibitors, sulfonylureas) 2. Hemophilia or any other bleeding disorder **3. History of >1 severe hypoglycemic event with seizure or loss of consciousness in the last 3 months** 4. History of >1 DKA event in the last 6 months not related to illness, infusion set failure, or initial diagnosis 5. History of chronic renal disease or currently on hemodialysis 6. History of adrenal insufficiency 7. Hypothyroidism that is not adequately treated in the opinion of the investigator 8. Use of oral or injectable steroids within the last 8 weeks **9. Known, ongoing adhesive intolerance** 10. Plans to receive blood transfusions or erythropoietin injections during the course of the study I I. A condition, which in the opinion of the investigator or designee, would put the participant or study at risk 12. Participation in another pharmaceutical or device trial at the time of enrollment or during the study 13. Having immediate family members employed by Tandem Diabetes Care, Inc. or Dexcom, Inc., or having a direct supervisor at place of employment who is also directly involved in conducting the clinical trial (as a study investigator, coordinator, etc.); or having a first-degree relative who is directly involved in conducting the clinical trial
Sample Size	Up to 45 screened participants with the goal of at least 30 participants completing the study pump use period
Intervention	t:slim X2 with Control-IQ Technology and t:connect mobile application with mobile bolus capabilities and Study CGM
Participant Duration	-8 weeks
Study Duration (planned)	-8 months from first enrollment until last participant visit
Protocol Overview/Synopsis	After consent is signed, eligibility will be assessed. Eligible participants will proceed to the main study described below. Initial pump parameter settings will be reviewed by clinical site staff after uploading baseline personal CGM and insulin data to a web-based AI-driven Advisor interface. The Advisor will suggest pump parameter settings that the study investigator may either accept unchanged or else override based on clinical judgment if there are any safety concerns. A study pump will be configured with the resulting parameter values, the participant will be provided with the study pump and study CGM and other supplies and the participant will begin home use of the pump. Visits will occur at 3 days and at 1, 2, 4, and 6 weeks, with each visit including site upload of pump/CGM data to the Advisor interface to obtain recommended adjustments to pump parameters. As before, the study investigator may either accept unchanged or else override based on clinical judgment if there are any safety concerns. A final study visit will occur at 8 weeks, at which time the study participant will be transitioned back to preferred post-study insulin therapy. A follow-up safety visit will occur 3 days after the final visit to confirm successful transition to post-study insulin therapy. • ***All study visits may be conducted either remotely via teleconference or else in person at***

PARTICIPANT AREA	DESCRIPTION
	the clinical site

The following table provides an overview of the schedule of study visits, phone contacts, and key procedures.

Table 2. Schedule of Study Visits and Procedures

	Screening Visit*	Baseline - **Pump Initiation****	3d	1w	**1w**	4w	6w	8w	8w +3d
Informed Consent	**X**								
Eligibility Assessment	**X**								
Medical history/ height/weight	**X**								
Central lab HbAlc		X							
Study pump training		X							
Upload device data from home			X	X	X	X	**X**	**X**	
Review diabetes management, **AEs and medications**		X	X	X	X	X	**X**	**X**	X
Manual pump parameter adjustment only if safety issue			Any scheduled or unscheduled visit						
AI-driven pump parameter initiation/adjustment		X	X	X	X	X	**X**		

• All screening visit procedures must be completed within 28 days of eConsent.

•• All Pump initiation visit procedures must be completed within 10 days of screening visit procedure completion.

2 Consistency

This SAP is consistent with the study protocol statistics chapter (version indicated on the title page).

3 Statistical Hypotheses

The primary outcomes for this study are safety outcomes: hypoglycemia and hyperglycemia measured by adverse events and CGM. Statistical hypotheses are stated for the CGM-measured outcomes only.

CGM-measured percentage below 54 mg/dL and CGM-measured percentage above 250 mg/dL will be tested for non-inferiority over an 8-week period.

The null/alternative hypotheses are:

Percentage below 54 mg/dL:

a. *Null Hypothesis:* The difference in mean CGM-measured % below 54 mg/dL between the 8 weeks follow-up and baseline is greater than or equal to +0.5% (non-inferiority).
b. *Alternative Hypothesis:* The difference in mean CGM-measured % below 54 mg/dL between the 8 weeks follow-up and baseline is less than +0.5%.

Percentage above 250 mg/dL:

a. *Null Hypothesis:* The difference in mean CGM-measured % above 250 mg/dL between the 8 weeks follow-up and baseline is greater than or equal to +3% (non-inferiority)
b. *Alternative Hypothesis:* The difference in mean CGM-measured % above 250 mg/dL between the 8 weeks follow-up and baseline is less than +3%.

4 Sample Size

The study has not been formally powered to test any a priori hypothesis. The goal is to have at least 30 participants complete the 8-week trial period. Some outcomes will be compared between these participants and a sample of participants from the prior PEDAP study.

S Outcome Measures

5.1 Safety Endpoints

- Severe Hypoglycemia (SH) events and SH event rate per 100 person-years
- Diabetic ketoacidosis (DKA) events and DKA event rate per 100 person-years
- Reportable hyperglycemia adverse events with or without ketosis
    - Events related to the study device
    - Events not related to the study device
- Reportable hypoglycemia adverse events that are not severe
- Number of calendar days with any ketone level:::1.0 mmol/L

Hierarchical Safety Endpoints

- CGM-Measured
    - % Time >250 mg/dL (non-inferiority)
    - % Time <54 mg/dL (non-inferiority)

Additional Safety Endpoints

- Other serious adverse events
- Any adverse event rate per 100 person-years
- Adverse device effects (ADE)
- Serious adverse device events (SADE)
- Unanticipated adverse device effects (UADE)

5.2 Efficacy Endpoints

Hierarchical Efficacy Endpoints (tested for superiority compared with baseline)

- CGM-Measured
  - % Time in range 70-180 mg/dL
  - Mean glucose
  - % Time >250 mg/dL
  - % Time <70 mg/dL
  - % Time <54 mg/dL

Secondary Endpoints

- CGM-Measured
  - % Time in range 70-140 mg/dL
  - % Time >180 mg/dL
  - % Time >300 mg/dL
  - % Time <60 mg/dL
  - Glucose standard deviation
  - Glucose coefficient of variation
  - High blood glucose index (HBGI)
  - Low blood glucose index (LBGI)
  - Weekly hyperglycemic event rate
  - Weekly hypoglycemic event rate
  - Binary
    - % Time in range 70-180 mg/dL improvement from baseline to 8 weeks:::5%
    - % Time in range 70-180 mg/dL improvement from baseline to 8 weeks:::10%
    - % Time in range 70-180 mg/dL >70% and % time <70 mg/dL <4%
- Insulin
  - Total daily insulin (units/kg)
  - Percentage of total insulin delivered via basal

Exploratory Endpoints

- Insulin
  - Total daily basal insulin (units/kg)
  - Total daily bolus insulin (units/kg)
  - Total daily manual bolus (units/kg)
  - Total daily automated bolus (units/kg)
  - Number of manual insulin doses **per** day
  - Number of manual insulin doses with carb announcement **per** day
  - Average daily profile basal rate divided by total daily insulin in percentage points
  - Average carbohydrate ratio daily profile (C:I) multiplied by total daily insulin
  - Average insulin sensitivity factor daily profile (G:I) multiplied by total daily insulin

5.3 Analysis Datasets and Sensitivity Analyses

To be included in included in analyses of CGM and insulin outcomes, participants must provide at least 168 hours of CGM data for each of the baseline and trial phase and spend at least 50% of the study period in closed-loop mode.

All participants who enroll in the PEDAP-AI study will be included in the safety analyses of endpoints that are not measured by CGM. Analyses will include all events that occur between enrollment and the 3-Day Post-Study Safety contact or the end of the 71$_{st}$ day after the date of the Closed Loop Initiation visit- whichever is earlier. For participants who do not complete the study, the date of the final contact will be used in place of the 3-Day Post-Study Safety contact date.

5.4 CGM Mehics Calculations

Baseline values for each CGM metric will be computed from the most recent 28 days of CGM data before the Screening visit.

During the treatment period, CGM metrics will be calculated from the beginning of study pump use until the end of the day before the 8-Week visit date or the end of the 59th day after the date of the Closed Loop Initiation visit- whichever is earlier. For participants who do not complete the study, the date of the final contact will be used in place of the 8-Week visit date.

A CGM-measured hypoglycemic event is defined as 15 consecutive minutes with a sensor glucose value below 54 mg/dL. At least 2 sensor values <54 mg/dL that are 15 or more minutes apart plus no intervening values :::54 mg/dL are required to define an event. The end of the hypoglycemic event is defined as a minimum of 15 consecutive minutes with a sensor glucose concentration :::70 mg/dL. At least 2 sensor values :::70 mg/dL that are 15 or more minutes apart with no intervening values <70 mg/dL are required to define the end of an event.

A CGM-measured hyperglycernic event is defined as 90 consecutive minutes with a sensor glucose value above 300 mg/dL. At least 2 sensor values >300 mg/dL that are 90 or more minutes apart plus no intervening values $300 mg/dL are required to define an event. The end of the hyperglycernic event is defined as a minimum of 15 consecutive minutes with a sensor glucose concentration ::,180 mg/dL. At least 2 sensor values::,180 mg/dL that are 15 or more minutes apart with no intervening values >180 mg/dL are required to define the end of an event.

5.5 Calculation of Insulin Metlics

Insulin metrics for comparisons between baseline and follow-up describe the seven days prior to the visits.

Baseline insulin metrics will use data reported from the Diabetes Screening CRF. Insulin metrics will be calculated at 8 weeks using Tandem pump data. Insulin pump data on at least 5 of 7 days will be required to calculate insulin metrics. Weight will only be recorded at the Screening visit. All calculations of units/kg will use this weight.

5.6 Calc ula tion of CGM and Insulin Metlics for Comparison with the PEDAP Histor ical Conti·ol Group

Results from this PEDAP-AI study will be compared with those from a sample of participants from the prior PEDAP study. For this analysis, participants from the prior PEDAP study will be limited to those whose RCT baseline HbAlc values are no more than 0.2 percentage points outside of the range observed among the PEDAP-AI participants. Basdine metrics for the PEDAP historical control group will be as reported for the PEDAP RCT.

The follow-up period for these comparisons will be the 7m and gm weeks of study pump use. For PEDAP-AI participa,ntsthis will be the period from the adjustment of pump settings at the 6-Week visit until the end of the day before the 8-Week visit. If the 6-Week visit is missed, data from the 14 days before the 8-Week visit will be used. PEDAP-AI participants will be excluded from these analyses if they miss the 8-Week visit. For the PEDAP historical control group, follow-up metrics will be calculated from the 14 days prior to the 56m day after the date of the beginning of study pump use. These data will come from the RCT phase for those who were assigned to the CLC group and Extension phase for those who were assigned to the SC group. Participants must have spent at least SO% of the time between pump initiation and the end of the follow-up period in closed-loop mode, and provided at least 168 hours of data in both the baseline and follow-up periods for inclusion in analyses.

Baseline insulin metrics will use data reported from the Diabetes Screening CRF. Insulin data must be present on at least 70% of follow-up days to calculate insulin metrics. The day of the 6-Week visit will be excluded from the calculation of PEDAP-AI participants' insulin metrics. Calculation of units/kg will use the weight from the Screening visit only.

5.7 Analysis \Vindows

For any analysis or tabulation that involves HbAlc measured at the Closed Loop Initiation visit, the sample must be collected no earlier than three days prior to the visit and no later than 21 days after the visit.

6 Analysis

6.1 Analysis of the Hiera rchical Endpoints

Summary statistics will be reported for the hierarchical endpoints at baseline and during follow-up as well as for differences from baseline. 24-hr profile plots will be drawn for follow-up. Boxplots will be drawn for baseline and follow-up. Scatter plots will be drawn for follow-up versus baseline. 95% confidence intervals will be constructed for the change from baseline to 8 weeks. For% <54 mg/dL and% >250 mg/dL, tests of non-inferiority will be conducted using paired *t-tests*. The limits will be 0.5% for% <54 mg/dL and 3% for%>250mg/dL. If these outcomes are determined to be non-inferior, they will be tested for superiority in a hierarchy with% 70-180 mg/dL, mean gluco,se and% <70 mg/dL. Tests of superiority will be two-sided paired *t-tests*. If the distribution of changes is skewed then robust methods will be used instead.

To preserve the overall type 1 error among the formal comparisons, a hierarchy will be used in the following order:

- CGM% >250 mg/dL (non-inferiority; limit= 3%)
- CGM% <54 mg/dL (non-inferiority; limit = 0.5%)
- CGM% 70-180mg/dL(superiority)
- Mean glucose (superiority)
- CGM% >250 mg/dL (superiority)
- CGM% <70 mg/dL (superiority)
- CGM% <54 mg/dL (superiority)

If any of these comparisons result in a p-value >0.05, then formal testing will stop and p-values will not be generated for any subsequent tests on the list. Note that the point estimates and confidence intervals will be generated for metrics regardless of statistical significance.

6.2 Analysis of Secondary Endpoints

6.2.1 Comparison with Baseline

Summary statistics will be reported for baseline, follow-up, and difference from baseline. For all continuous outcomes, boxplots will be drawn for baseline and follow-up and scatter plots will be drawn for follow-up versus baseline. 24-hr profile plots will be drawn for continuous CGM-measured endpoints during follow-up.

Change over time will be compared with a paired *t-test* when the change appears approximately normal, and using robust methods when the change is skewed. Ninety-five percent confidence intervals of the changes from baseline will be derived from these tests.

For the binary outcome% time in range 70-180 mg/dL>70% and% time <70 mg/dL <4,% the proportion will be compared between baseline and follow-up with Barnard's exact test. A ninety-five percent confidence interval of the change from baseline will be derived from this test.

6.2.2 Comparison with PEDAP Hist01ical Control

Comparisons between the PEDAP-AI group and the PEDAP historical control group will be made for all of the hierarchical and secondary efficacy endpoints listed above. Continuous endpoints will be compared between the PEDAP-AI and PEDAP cohorts using a linear model adjusting for the baseline value, age at initiation of closed loop use, use of pump or MDI before initiation of closed loop use, and clinical center as fixed effects. Binary endpoints will be compared using a logistic model that adjusts for the same effects. Summary statistics for baseline, follow-up, and change from baseline will be reported by study along with the adjusted differences between the studies and their 95% confidence intervals. Boxplots displaying baseline and follow-up for both groups will be drawn for continuous outcomes.

6.3 Analysis of Exploratory Endpoints

No p-values will be calculated for exploratory analyses. Summary statistics for total daily basal insulin and total daily bolus insulin will be tabulated for baseline, 8 weeks, and change from baseline to 8 weeks. For all other outcomes, summary statistics will be tabulated for 8 weeks. Boxplots for the follow-up period will be drawn for all outcomes. Boxplots for baseline will be given for total daily basal insulin and total daily bolus insulin. Summary statistics for the final 2-week period will be displayed side-by-side with those of the PEDAP historical control group.

6.4 Additional Tabulations and Plots

Summary statistics will be tabulated by daytime (6:00 am - 9:59 pm) and nighttime (10:00 pm - 5:59 am) during baseline and the 8 weeks of follow-up for each of the continuous CGM-measured outcomes listed in 5.2.

During the trial period, the closed-loop system will include a periodic parameter adjustment driven by an AI-based Advisor system. Tabulations, 24-hour profile plots and boxplots of the continuous CGM-measured outcomes listed in 5.2 will be generated for each of the six adaptation periods and the two 4-week periods of the study.

The end of the first 4-week period will be the adjustment of pump settings at the 4-Week visit. The end of the second 4-week period will be the end of the day before the 8-Week visit date or the end of the 59th day after the date of the Closed Loop Initiation visit- whichever is earlier. This date will also serve as the end of the sixth adaptation period, which will begin at the 6-Week visit. The other five adaptation periods will include data from the adjustment of pump settings at the visit until the adjustment of pump settings at the subsequent visit. If the subsequent visit is missed or out-of-window, the end of the period will be the end of the day on the latest date that would be in-window for the visit. If a participant misses a visit they will be absent from the period begun by that visit. Participants must provide CGM data for at least 75% of the time period to be included in the plots and tabulations for that time period.

7 Safety Analyses

Hierarchical safety endpoints will be analyzed according to the directions in 6.1. All safety endpoints listed in 5.1 will be summarized in tables. Details of each reportable adverse event will be provided in a listing.

8 Intervention Adherence

The following will be tabulated for the 8-week study period to assess intervention adherence:

- Percent time of CGM sensor use
- Percent time of closed-loop system use
- Percent time in different operational modes
- Percent of AI recommendations that are accepted without any study physician adjustments
    - For AI recommendations that are adjusted, tabulation of initial and adjusted values

System use metrics will be calculated from the beginning of study pump use until the end of the day before the 8-Week visit date or the end of the 59th day after the date of the Closed Loop Initiation visit- whichever is earlier. For participants who do not complete the study these metrics will be prorated: the date of the final contact will be used in place of the 8-Week visit date.

9 Protocol Adherence and Retention

The following tabulations and analyses **will** be performed to assess protocol adherence for the study:

- Number of protocol and procedural deviations
- Flowchart accounting for all enrolled participants
- Flowchart of all participants at all scheduled visits and phone contacts after treatment initiation
- Number of and reasons for unscheduled visits and phone calls

- Number of participants who stopped treabnent and reasons

10 Baselin e Desa i ptive Statistics

Baseline demographic and clinical characteristics of all participants included in the primary analysis will be summarized in a table using summary statistics appropriate to the distribution of each variable. Characteristicswill include:

- Age
- Diabetes duration
- BMI percentile
- Sex
- Race/ethnicity
- Parents' highest education level
- Annual household income
- Health insurance
- HbAlc at initiation of closed loop use
- Insulin modality
- Total daily insulin (units/kg)
- Number of injections of short-acting insulin per day
- Number of diabetic ketoacidosis events in the past 12 months
- Number of severe hypoglycemia events in the past 12 months

11 Device Issues

The following will be tabulated for the 8-week study period to assess device issues:

- Device malfunctions requiring study team contact and other reported device issues
- Rate of different failure events and alarms per 24 hours recorded by the Control-IQ system

Tabulations will include all events that occur between enrollment and the 3-Day Post-Study Safety contact or the end of the 71" day after the date of the Closed Loop Initiation visit- whichever is earlier. Details of device issues will be provided in a listing.

12 Planned Inte1i m An al yses

No formal interim efficacy analyses are planned.

The DSMB will review safety data at intervals, with no formal stopping rules.

13 Su bgro up An alyses

With only 30 participants, the ability to evaluate subgroups is limited. However, percentage of timespent >250 mg/dL and% of timespent <54 mg/dL over 8 weeks will be explored separately in baseline HbA1c, race/ethnici,ty MDI or pump use at enrollment, and sex. No p-values will be calculated for these analyses.

14 Missing Data

All comparisons will be restricted to available cases.

15 Multiple Compa1isons/Multiplicity

For the baseline versus follow-up comparisons of the metrics mentioned in 6.1, the overall type **I** error will be preserved using the hierarchical procedure described above. For all other analys,es the false discovery rate will be controlled using the adaptive Benjamini-Hochberg procedure.[1] The categories for the FDR correction will be:

- Baseline vs follow-up for CGM-measured endpoints
- Baseline vs follow-up for insulin endpoints
- PEDAP-AI vs PEDAP for CGM-measured endpoints
- PEDAP-AI vs PEDAP for insulin endpoints

16 References

1. Benjamini Y, Hochberg Y. On the adaptive control of the false discovery rate in multiple testing with independent statistics. *Journal of Educational and Behavioral Statistics.* 2000;25(1):60-83.