

ASPIRE In-Home: Rationale, Design, and Methods of a Study to Evaluate the Safety and Efficacy of Automatic Insulin Suspension for Nocturnal Hypoglycemia

David C. Klonoff, M.D., FACP,¹ Richard M. Bergenstal, M.D.,² Satish K. Garg, M.D.,³ Bruce W. Bode, M.D., FACE,⁴ Melissa Meredith, M.D.,⁵ Robert H. Slover, M.D.,³ Andrew Ahmann, M.D.,⁶ John B. Welsh, M.D., Ph.D.,⁷ and Scott W. Lee, M.D.⁷

Abstract

Nocturnal hypoglycemia is a barrier to therapy intensification efforts in diabetes. The Paradigm[®] Veo[™] system may mitigate nocturnal hypoglycemia by automatically suspending insulin when a prespecified sensor glucose threshold is reached. ASPIRE (Automation to Simulate Pancreatic Insulin REsponse) In-Home (NCT01497938) was a multicenter, randomized, parallel, adaptive study of subjects with type 1 diabetes. The control arm used sensor-augmented pump therapy. The treatment arm used sensor-augmented pump therapy with threshold suspend, which automatically suspends the insulin pump in response to a sensor glucose value at or below a prespecified threshold. To be randomized, subjects had to have demonstrated ≥ 2 episodes of nocturnal hypoglycemia, defined as >20 consecutive minutes of sensor glucose values ≤ 65 mg/dl starting between 10:00 PM and 8:00 AM in the 2-week run-in phase. The 3-month study phase evaluated safety by comparing changes in glycated hemoglobin (A1C) values and evaluated efficacy by comparing the mean area under the glucose concentration time curves for nocturnal hypoglycemia events in the two groups. Other outcomes included the rate of nocturnal hypoglycemia events and the distribution of sensor glucose values. Data from the ASPIRE In-Home study should provide evidence on the safety of the threshold suspend feature with respect to A1C and its efficacy with respect to severity and duration of nocturnal hypoglycemia when used at home over a 3-month period.

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Background

The choice of insulin delivery systems for the treatment of type 1 diabetes has evolved rapidly as a result of innovations in pumps, continuous glucose monitoring (CGM) sensors, and control algorithms. In spite of this, many patients are unable to achieve a lower rate of nocturnal hypoglycemia while reaching and maintaining recommended glycated hemoglobin (A1C) values. An important advance aimed at preventing or mitigating hypoglycemia is the

Author Affiliations: ¹Mills-Peninsula Health Services, San Mateo, California; ²International Diabetes Center, Minneapolis, Minnesota; ³University of Colorado School of Medicine, Aurora, Colorado; ⁴Atlanta Diabetes Associates, Atlanta, Georgia; ⁵University of Wisconsin, Madison, Wisconsin; ⁶Oregon Health and Sciences University, Portland, Oregon; and ⁷Medtronic, Inc., Northridge, California

Abbreviations: (A1C) glycated hemoglobin, (AUC) area under the curve, (CGM) continuous glucose monitoring, (FDA) Food and Drug Administration, (HFS) hypoglycemia fear survey, (LGS) low glucose suspend

Keywords: ASPIRE, insulin pump suspension, low glucose suspend, nocturnal hypoglycemia, randomized controlled trial, threshold suspend

Corresponding Author: David C. Klonoff, M.D., FACP, Mills-Peninsula Health Services, 100 S. San Mateo Dr., Room 5147, San Mateo, CA 94401; email address dklonoff@diabetestechnology.org

low glucose suspend (LGS) feature of the Paradigm® Veo™ system (Medtronic, Inc., Northridge, CA), first introduced outside the United States in 2009. When the feature is in use, it responds to CGM values at or below a prespecified limit by suspending the pump for up to 2 h. Initial experience with the LGS feature has been favorable¹ and has been documented in several published studies. A 3-week user evaluation of 31 adults showed that nocturnal hypoglycemia was reduced in those at greatest risk by use of the LGS feature and that subjects found it useful and wanted to continue using it.² A study of 21 children and adolescents found that use of the feature was associated with fewer hypoglycemic excursions.³ Interim results of an ongoing hypoglycemia prevention study of 24 adults and children showed that, when the pump suspended for 2 h at night, sensor glucose values recovered to a mean of 99 mg/dl at the end of the pump suspension event and to 155 mg/dl 2 h after insulin resumption.⁴ A retrospective analysis of pump and sensor data showed that use of the LGS feature was associated with fewer sensor glucose values in the hypoglycemic range, as well as in the severe hyperglycemic range and that 2 h pump suspension events did not result in severe rebound hyperglycemia.⁵ The first randomized, controlled, crossover study of the LGS feature was the ASPIRE (Automation to Simulate Pancreatic Insulin REsponse) In-Clinic study, which established its efficacy with respect to reducing the duration and severity of exercise-induced hypoglycemia in an inpatient setting.^{6,7} Most of the prior studies had been for less than 3 months,^{2,3,6,7} included relatively few subjects,^{3,4} or did not evaluate changes in average glycemia from baseline.^{2,3,6,7}

In the United States, the LGS feature is currently under review by the Food and Drug Administration (FDA) as the threshold suspend feature. Both the LGS and the threshold suspend features allow for insulin suspension of up to 2 h based on sensor glucose values that do not require confirmation. Although the commercial feature of the Veo pump is called LGS, in this article, we refer to this feature as threshold suspend because the suspension of insulin is based on the sensor glucose value reaching a preset threshold.

The ASPIRE In-Home study was designed to evaluate the safety and efficacy of the threshold suspend feature. In contrast to the ASPIRE In-Clinic study,^{6,7} ASPIRE In-Home was of longer duration, was conducted in the home setting, evaluated spontaneous rather than induced hypoglycemia, and used sensor glucose values rather than frequently sampled plasma glucose values to quantify hypoglycemia. Here we provide methodological details of the ASPIRE In-Home study.

Methods

Design and Enrollment

The study allowed for screening of up to 2000 subjects based on an anticipated high failure rate due to subjects failing to comply with sensor wear and/or nocturnal hypoglycemia requirements during the run-in phase. It was anticipated that 260 subjects would be randomized to establish the safety end point. An adaptive design was used for the efficacy end point. After 100 subjects completed the study, an independent statistician was to perform an interim analysis of the efficacy end point to re-estimate the sample size required for the efficacy end point. The protocol encouraged recruitment of subjects representing a variety of ethnicities and body mass indices. Centers were to include pediatric subjects (aged 16–21 years) as 20% of their study cohorts. The protocol was developed by Medtronic and finalized with guidance from the FDA and from the study's principal investigators. Adult subjects were to be enrolled throughout the study. Data from the first 10 adults in the threshold suspend group were used by the data safety and monitoring board to determine that it was safe to enroll pediatric subjects (aged 16–21 years) and subjects with significant cardiovascular history. Inclusion and exclusion criteria are summarized in **Table 1**. The intention-to-treat population included all randomized subjects. The per-protocol population included all randomized subjects who completed the trial without any major deviations and who had worn the sensor for >80% of the time and who had the correct suspend setting during the study phase for >80% of the time. For subjects in the threshold suspend group who turned the feature off during the study, the interval that the feature was turned off was not included in the per-protocol analysis.

Visit Schedule

As shown in **Figure 1**, the study included a run-in phase, a randomization step, and a study phase in seven visits. The first visit (day 0) was to include consent and screening to assess eligibility for the run-in phase and collection

Table 1.
Inclusion and Exclusion Criteria

Inclusion criteria, run-in phase	
	Age 16–70 years (subjects aged 16–21 years must have appropriate support system to be determined by the investigator)
	Psychological soundness
	Age <40 years at disease onset
	Diagnosed with type 1 diabetes ≥2 years prior to screening
	Negative stimulated C-peptide test
	Willingness to perform ≥4 finger stick blood glucose measurements daily
	Willingness to perform required sensor calibrations
	Willingness to wear the system continuously throughout the study
	Willingness to keep a log to record—at minimum—sick days, days with exercise, and days with symptoms of low glucose
	A1C from 5.8% to 10.0%
	Pump therapy for >6 months
	Under the care of diabetes health care provider(s) for 6 months or more
	Ability and willingness to upload data on a weekly basis
	Adequate treatment for celiac disease, if it exists
	Use of insulin lispro or insulin aspart and ability to pay for them
Inclusion criteria, study phase	
	During the run-in phase, demonstrated sensor wear for ≥80% of the time
	During the run-in phase, at least two episodes of nocturnal hypoglycemia, defined as consecutive sensor glucose values ≤65 mg/dl for >20 min, starting between 10:00 PM and 8:00 AM, with no evidence of user–pump interaction
Exclusion criteria	
	History of >1 episode of severe hypoglycemia resulting in any of the following during the 6 months prior to screening: medical assistance, coma, or seizures
	Inability to tolerate tape adhesive in the area of sensor placement
	Unresolved adverse skin condition in the area of sensor placement
	Pregnancy or plans to become pregnant during the study
	Subject has a new diagnosis of myocardial infarction, unstable angina, coronary artery bypass surgery, coronary artery stenting, transient ischemic attack, cerebrovascular accident, angina, congestive heart failure, ventricular rhythm disturbances, or thromboembolic disease
	Current treatment for hyperthyroidism
	Abnormal creatinine or thyroid-stimulating hormone value
	Oral, injectable, or intravenous steroids within 8 weeks from time of screening visit
	Participation in an investigational study (drug or device) in the past 2 weeks
	Hospitalization or emergency room visit in the 6 months prior to screening, resulting in a primary diagnosis of uncontrolled diabetes
	Currently abusing illicit drugs
	Currently abusing prescription drugs
	Currently abusing alcohol
	Use of pramlintide at time of screening
	History of visual impairment, which would not allow subject to participate in the study and perform all study procedures safely, as determined by the investigator
	Elective surgery planned that requires general anesthesia during the course of the study
	Is a shift worker with working hours between 10:00 PM and 8:00 AM
	Has a sickle cell disease or hemoglobinopathy or has received red blood cell transfusion

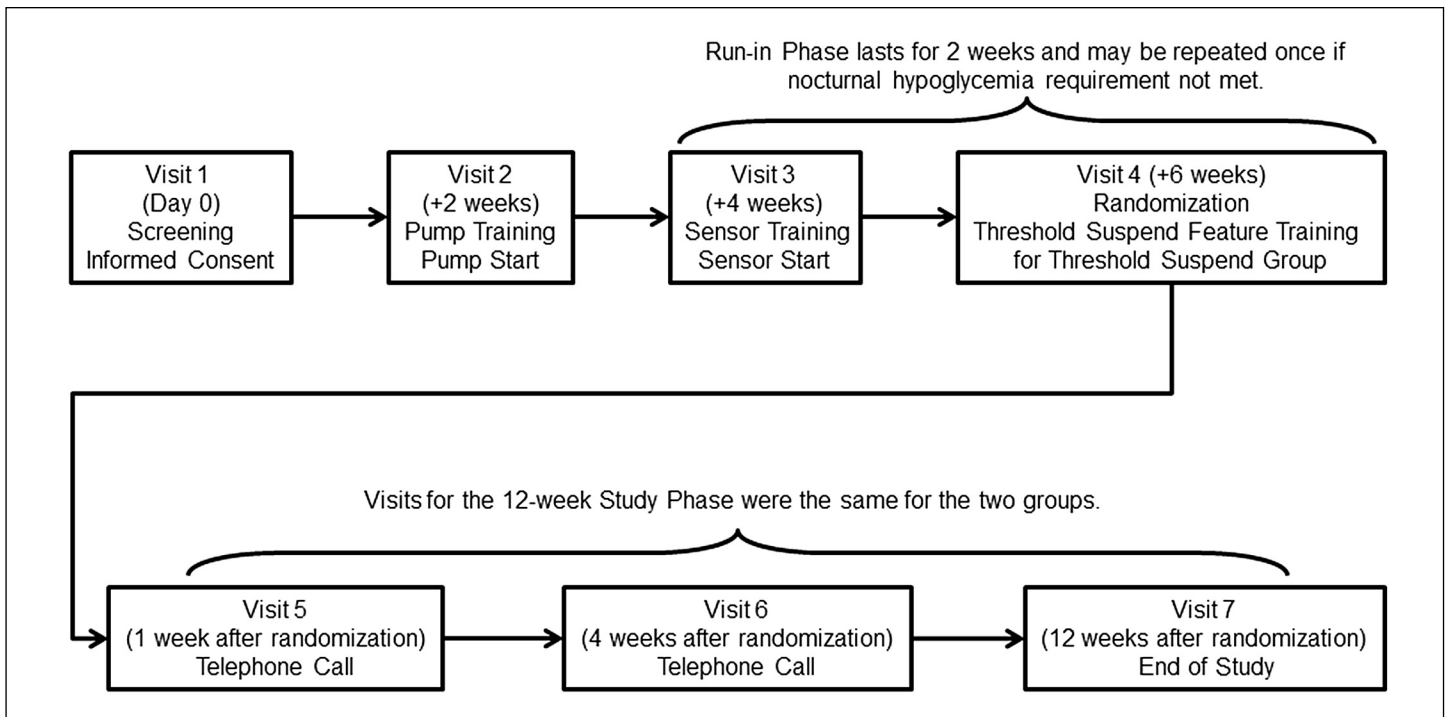


Figure 1. ASPIRE In-Home study visits.

of baseline and demographic data. Blood samples for A1C determination at a central NGSP-certified laboratory (Quest Diagnostics, Valencia, CA) were to be obtained at this time. Visit 2 (day 8 ± 6) included study training and device disbursement and training. All subjects were to receive Paradigm Revel 2.0 pumps for use throughout the run-in phase and Bayer CONTOUR[®] Next Link blood glucose meters for use throughout the study. Subjects were to be registered in the Medtronic CareLink[®] Therapy Management System for Diabetes at this time and instructed to upload pump, blood glucose meter, and CGM data at weekly intervals. Subjects were also to complete the hypoglycemia fear survey (HFS) and the EQ-5D questionnaires at this visit. Visit 3 (day 21 ± 7) was to include starting of CGM sensor wear with Enlite sensors and was the start of the 14-day sensor wear compliance window. Subjects were to be instructed to wear the sensors at all times. At visit 4 (day 35 ± 7), uploaded sensor data were to be used to establish eligibility for randomization, which required subjects to have successfully worn the sensors $\geq 80\%$ of the time (equivalent to 11.2 days of sensor data in the 14-day run-in phase) and to have experienced ≥ 2 episodes of nocturnal hypoglycemia. An episode of nocturnal hypoglycemia was defined as an interval lasting >20 min in which the sensor glucose value was ≤ 65 mg/dl that started between 10:00 PM and 8:00 AM and in which CareLink reports established that there was no user-pump interaction during the first 20 min. The run-in period could be repeated once if the nocturnal hypoglycemia requirement was not met. For subjects who met the sensor wear and nocturnal hypoglycemia requirements, visit 4 also served as the randomization visit. Subjects were to be randomized to either the control group (sensor-augmented pump therapy) or the threshold suspend group. Each subject in the threshold suspend group was to be switched to a Paradigm Veo insulin pump with its autocalibration feature disabled, its maximum bolus setting at ≤ 25 U, and the pump suspension threshold set to 70 mg/dl. Subjects in the threshold suspend group could adjust the sensor glucose value at which pump suspension occurred to values between 60 and 90 mg/dl and were to be instructed to have the threshold suspend feature on during the 10:00 PM to 8:00 AM interval. Subjects in the control group were to continue to use the Paradigm Revel 2.0 pump. Subjects were to be instructed to calibrate sensors 3–4 times spread out throughout the day.

Visit 5 (day 42 ± 6 ; 1 week postrandomization) and visit 6 (day 63 ± 7 ; 4 weeks postrandomization) were to be conducted via telephone to assess whether any adverse events had occurred, to ask subjects about device performance issues, and to provide subjects with the opportunity to bring up study-related questions and concerns. Visit 7 (day 118 ± 7 ; 12 weeks postrandomization) was the end-of-study visit, during which study devices were to be returned, CareLink

clinical reports were to be reviewed, blood was again to be collected for A1C determination at an NGSP-certified central laboratory, and the HFS and EQ-5D surveys were to be completed again. For subjects who repeated the 2-week run-in phase in order to meet randomization criteria, visits 5–7 were to be conducted on study days 56 ± 6 , 77 ± 7 , and 133 ± 7 , respectively.

Primary and Secondary Outcomes

All analyses were performed with the intention-to-treat population data set, which included all randomized subjects. The primary safety end point was the change in A1C from baseline. Mean changes in A1C concentrations were estimated, and the group difference was tested with a noninferiority margin of 0.4% and a one-sided significance level of 0.025. The safety end point was tested with multiple imputations. The primary efficacy end point was the area under the sensor glucose concentration time curve [area under the curve (AUC)] for nocturnal hypoglycemia events. Only nocturnal hypoglycemia events that did not include a pump interaction (i.e., meter blood glucose entry, meal markers, insulin delivery change) in the first 20 min were not preceded within 20 min by a rapid (>5 mg/dl/min) rate of change of sensor glucose values and that lasted longer than 20 min after the first sensor glucose value ≤ 65 mg/dl were used in the analysis. Events separated by <30 min from one another were counted as a single event. The starting time for evaluable nocturnal hypoglycemia events was restricted to the hours between 10:00 PM and 8:00 AM. Event AUC data were analyzed with both original and log-transformed scales. The mean log-transformed event AUCs were estimated and compared by a superiority test with a one-sided significance level of 0.025.

The use of one-sided tests for the primary end points was based on discussions with the FDA. For the primary safety end point, only one direction of the test result was of interest (i.e., threshold suspend group–control group difference $<0.4\%$), and the one-sided significance level of 0.025 was equivalent to the normal significance level of 0.05 with a two-sided test. For the primary efficacy end point, a similar approach was used because the only outcome of interest was whether the mean AUC of nocturnal hypoglycemic events in the threshold suspend group was less than that of the control group.

Descriptive comparisons were to be performed for the following observations of interest. For exposure to hypoglycemia and hyperglycemia, the AUC and time spent at or below various sensor glucose cutoff values were to be compared between groups. For the threshold suspend group, threshold suspend events were to be characterized by their diurnal distribution, duration, and associated settings and sensor glucose values and (when available) clinical symptoms. The incidence of diabetic ketoacidosis and severe hyperglycemia were to be compared between groups, as was the incidence of infusion set catheter blockage, glycemic control during periods of illness versus no illness reported, incidence of seizures, glycemic variability from sensor glucose data, mean sensor and blood glucose values, sensor compliance, daily calibration frequencies, and setting and activation of predictive and reactive alerts. Health and wellbeing outcomes of interest were to include results from the HFS and EQ-5D questionnaires.

Conclusions

Nocturnal hypoglycemia remains an important barrier in implementing therapy adjustments in subjects with type 1 diabetes.⁸ Severe nocturnal hypoglycemia can be catastrophic,^{9,10} and recurrent hypoglycemia can degrade subjects' cognitive¹¹ and autonomic¹² responses to subsequent hypoglycemic episodes.

Other methods to prevent or mitigate nocturnal hypoglycemia are in development. In particular, algorithms that suspend the pump in response to predicted hypoglycemia may provide more opportunities for hypoglycemia avoidance.^{13,14} The LGS feature represents an important advance in insulin delivery systems because of its safety and its association with reductions in hypoglycemia. Results from the ASPIRE In-Home study should provide solid evidence on the safety and efficacy of automatic insulin pump suspension. This study will be the first to quantify these effects in a randomized controlled trial of a well-defined population of subjects who are predisposed to nocturnal hypoglycemia, and its results will provide a benchmark for further studies of automated insulin delivery systems.

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Disclosures:

David Klonoff is a consultant to Google, InsuLine, Roche, and Sanofi. Richard Bergenstal has served on a scientific advisory board of, consulted for, or performed clinical research with Abbott Diabetes Care, Amylin, Bayer, Becton Dickinson, Boehringer Ingelheim, Bristol-Myers Squibb/Astra Zeneca, Intuity, Calibra, DexCom, Eli Lilly, Halozyme, Helmsley Trust, Hygieia, Johnson & Johnson, Medtronic, Merck, the National Institutes of Health, Novo Nordisk, ResMed, Roche, Sanofi and Takeda. Dr. Bergenstal's employer, non-profit Park Nicollet Institute, contracts for his services, for which he receives no personal income. He has inherited Merck stock and has been a volunteer of the American Diabetes Association and JDRF. Satish Garg has received speaking fees from Eisai, Johnson & Johnson, Medtronic, Novo Nordisk, Roche Diagnostics, and Sanofi and research grants from Cebix, Eli Lilly, Halozyme, MannKind, Medtronic, and Sanofi but holds no stock or equity in any device or pharmaceutical company. Bruce Bode has received consultant and speaker fees from Medtronic. Robert Slover is a member of the advisory board for Medtronic. Andrew Ahmann is a consultant on the advisory board for Medtronic (and also received research funding but only related to the protocol involved), and has also consulted for Novo and Sanofi. John Welsh and Scott Lee are employees of Medtronic

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