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ORIGINAL ARTICLE

Safety and Feasibility of the OmniPod Hybrid Closed-Loop System in Adult, Adolescent, and Pediatric Patients with Type 1 Diabetes Using a Personalized Model Predictive Control Algorithm

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Abstract

Background: The safety and feasibility of the OmniPod personalized model predictive control (MPC) algorithm in adult, adolescent, and pediatric patients with type 1 diabetes were investigated.

Methods: This multicenter, observational trial included a 1-week outpatient sensor-augmented pump open-loop phase and a 36-h inpatient hybrid closed-loop (HCL) phase with announced meals ranging from 30 to 90 g of carbohydrates and limited physical activity. Patients aged 6–65 years with HbA1c between 6.0% and 10.0% were eligible. The investigational system included a modified version of OmniPod, the Dexcom G4 505 Share® AP System, and the personalized MPC algorithm running on a tablet computer. Primary endpoints included sensor glucose percentage of time in hypoglycemia <70 mg/dL and hyperglycemia >250 mg/dL. Additional glycemic targets were assessed.

Results: The percentage of time <70 mg/dL during the 36-h HCL phase was mean (standard deviation): 0.7 (1.7) in adults receiving 80% meal bolus (*n* = 24), and 0.7 (1.2) in adults (*n* = 10), 2.0 (2.4) in adolescents (*n* = 12), and 2.0 (2.6) in pediatrics (*n* = 12) receiving 100% meal bolus. The overall hypoglycemia rate was 0.49 events/24 h. The percentage of time >250 mg/dL was 8.0 (7.5), 3.6 (3.7), 4.9 (6.3), and 6.7 (5.6) in the study groups, respectively. Percentage of time in the target range of 70–180 mg/dL was 69.5 (14.4), 73.0 (15.0), 72.6 (15.5), and 70.1 (12.3), respectively.

Conclusions: The OmniPod personalized MPC algorithm performed well and was safe during day and night use in adult, adolescent, and pediatric patients with type 1 diabetes. Longer term studies will assess the safety and performance of the algorithm under free living conditions with extended use.

Keywords: Artificial pancreas, Automated insulin delivery, Closed loop, Hybrid closed loop, OmniPod, Tubeless insulin pump.

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Introduction

CLOSED-LOOP ARTIFICIAL PANCREAS (AP) systems have been in development for several years, all with the goal of reducing the burden of diabetes through automated insulin delivery. Advances in microelectronics and glucose sensor technology and the U.S. Food and Drug Administration's (FDA) decision to make the development of closed-loop systems a priority have resulted in rapid advances in this field.[1,2] The first commercial closed-loop device was recently approved by the FDA in September 2016,[3] following a 3-month clinical study of 124 subjects aged 14–75 years that demonstrated few serious or device-related adverse events.[4,5] A recent meta-analysis of randomized controlled trials has demonstrated that AP systems consistently improve glycemic control across age groups compared to continuous subcutaneous insulin infusion (CSII) with blinded continuous glucose monitoring (CGM) or with sensor-augmented pumps (SAP).[6] In the outpatient setting, the use of AP systems has resulted in a 12% increased time in range (70–180 mg/dL) and a 50% reduction in the time spent in hypoglycemia.[6]

There are several AP systems currently under development in both academic and commercial endeavors. Each system offers unique features in the configuration of pumps, glucose sensors, algorithms, functionality, user interface, and data management. Systems are also differentiated by having single- or dual-hormone delivery.[1]

Early feasibility studies of the OmniPod® Horizon Automated Glucose Control system, a single-hormone hybrid closed-loop (HCL) system, are currently underway. The commercial system is intended to be a fully on-body device with a personalized Model Predictive Control (MPC) algorithm embedded in the OmniPod patch pump (Pod) communicating directly with the latest Dexcom CGM technology. A handheld device will transmit commands for insulin meal boluses, algorithm parameter adjustments such as change in target glucose and insulin delivery parameters, as well as allowing connection to a secure cloud server for data management.

The objectives of this feasibility study were to evaluate the safety and feasibility of the OmniPod personalized MPC algorithm in adult, adolescent, and pediatric patients with type 1 diabetes in a clinical research center setting.

Materials and Methods

This single-arm, observational clinical trial study was conducted at four sites and consisted of a 1-week, outpatient open-loop phase using SAP and a 36-h inpatient HCL phase using the OmniPod HCL investigational device.

During the open-loop phase, subjects managed their diabetes at home as per their usual routine using their personal insulin pump and the study CGM (Dexcom G4 505 Share® AP System). Investigators analyzed ∼7 days of open-loop data and adjusted pump settings for basal rate, insulin to carbohydrate ratio, and correction factor as needed, based on their clinical judgment, for safety before proceeding to the HCL phase.

The HCL phase began before breakfast on day 1 and concluded ∼4 h after lunch on day 2. The HCL phase included five meals with 30 to 90 g carbohydrate per meal, one overnight period, and limited physical activity. Subjects selected meals from a variety of food options with identical meals given for breakfast and lunch on days 1 and 2. During the HCL phase, subjects were closely monitored by study personnel. Hypoglycemia safety actions included treatment with 12 to 16 g of fast-acting carbohydrates for CGM values <70 mg/dL with a confirmatory fingerstick. A follow-up fingerstick was performed 15 min post-treatment to assess resolution, defined as blood glucose ≥70 mg/dL, or the need for additional treatment as per clinical standards. Fast-acting carbohydrates were also available to any subject who was symptomatic or requested treatment. Hyperglycemia treatment, a correction bolus target of 150 mg/dL, was initiated for CGM values of ≥300 mg/dL confirmed by fingerstick and ketones ≤1.0 mmol/L. HCL stopping criteria included blood glucose ≥300 mg/dL with ketones ≥3.0 mmol/L, subject unable to take oral carbohydrates, subject request, loss of consciousness, or seizure.

Pods were changed at the discretion of the investigator in cases of ketones >1.0 mmol/L or if there was a suspected infusion site failure. Subjects were discharged on day 2 when deemed safe by the investigators.

Two meal bolus protocols were used in the study. As this was the first human clinical study of the modified MPC algorithm, a conservative approach of 80% meal bolus was administered to the initial 24 adult subjects. The modified algorithm was determined to be safe and all subjects subsequently enrolled in the study received 100% meal bolus.

Subjects

Enrollment criteria include patients 6 to 65 years of age, type 1 diabetes for ≥1 year, HbA1c value >6% and <10% within the past 6 months, use of any insulin pump for ≥6 months, and total daily dose of insulin >0.4 U/kg. Patients with CGM experience were not excluded. Patients with ≥1 episode of severe hypoglycemia or diabetic ketoacidosis requiring an emergency room visit or hospitalization within the past 6 months or hypoglycemic unawareness assessed by the Clarke Questionnaire[7] were excluded. The study obtained institutional review board approvals and written informed consent from adults and the parents or guardians of minors. Written assent was obtained from all minors over ≥8 years of age.

Investigational device

System architecture. The investigational system used in this study consisted of a modified version of the Pod, a modified Personal Diabetes Manager (PDM), the Dexcom G4 505 Share AP System, and the personalized MPC algorithm running on a Windows 10 tablet configured with the portable AP System developed at the University of California at Santa Barbara.[8] Operationally, the Dexcom CGM receiver communicated with the portable AP System (tablet) via a wired USB connection. The portable AP System transmitted insulin dosing commands to the PDM via Bluetooth Low Energy relay. The PDM subsequently controlled insulin delivery by the Pod via a radiofrequency signal.

The user interface on the tablet clearly indicated to clinical study staff whether the system was in HCL mode or in open-loop mode. The tablet was used to start each Pod, initiate HCL, display CGM and insulin delivery data, and for meal bolus delivery and open-loop control, if needed.

Personalized MPC algorithm. The OmniPod personalized MPC algorithm is a specific implementation of the MPC algorithm that was originally developed at the University of California at Santa Barbara by Doyle, Dassau, and colleagues[9,10] The algorithm has undergone years of extensive study, with further enhancements made before its implementation in the present study. The OmniPod personalized MPC algorithm insulin-dosing decisions are made every 5 min based on CGM values to minimize the deviation between predicted blood glucose over a 60-min horizon and the target set point. Inputs to the algorithm include the subject-specific basal rate profile and total daily insulin dose. The algorithm incorporates an asymmetric cost function as described by Gondhalekar et al. to minimize the occurrence of hypoglycemia without compromising overall glycemic control.[11] A dynamic insulin-on-board constraint is dependent on the subject-specific insulin sensitivity factor to ensure that insulin delivery rates are limited for safety purposes. The algorithm set point for this study was a sensor glucose of 120 mg/dL.

Outcomes

Primary endpoints included safety parameters of percentage of time the sensor glucose was in a hypoglycemic range defined as <70 mg/dL and percentage time in a hyperglycemic range defined as ≥250 mg/dL during the HCL phase. Secondary endpoints included sensor mean glucose, percentage time ≤50, ≤60, 70 to 140, 70 to 180, ≥180, ≥300 mg/dL, standard deviation, and coefficient of variation (CV) of CGM values.[12]

Statistical analyses

As the endpoint for the study was safety, sample size was not determined. Prespecified descriptive statistical analyses were performed for all subjects who entered the study ($n = 58$). Results were summarized for the 36-h HCL study period (overall) and the overnight period defined as 23:00 to 07:00. The endpoints were summarized based on a modified intention-to-treat analysis that included subjects who entered the HCL phase of the study. Results for adult subjects who received 80% meal bolus were summarized separately from adults who received 100% meal bolus. Statistical analyses were performed using SAS® 9.3 (SAS Institute, Cary, NC).

Results

The characteristics of the 58 patients (adults $n = 34$, age ≥18 years; adolescents $n = 12$, 12 to <18 years; pediatrics $n = 12$, 6 to <12 years) are reported in Table 1. In the open-loop phase, 41 (70%) subjects had adjustments to their basal rate with increases made for 26 subjects and decreases made for 15 subjects. Changes were made to the insulin to carbohydrate ratios for 25 subjects (43%) with increases (decreased insulin delivery) in 4 subjects and decreases (increased insulin delivery) in 21 subjects. Correction factors were adjusted for 16 (28%) subjects with increases (decreased insulin delivery) in 6 subjects and decreases (increased insulin delivery) in 10 subjects. Glycemic measures for the open-loop phase are reported in Table 2.

Glycemic outcomes

Glycemic outcomes for the 36-h HCL phase overall and overnight are presented in Tables 3 and 4. The percentage of time in the hypoglycemic range <70 mg/dL for sensor glucose during the HCL phase overall was mean (standard deviation [SD]): 0.7 (1.7) in adults receiving 80% meal bolus ($n = 24$), and 0.7 (1.2) in adults ($n = 10$), 2.0 (2.4) in adolescents ($n = 12$), and 2.0 (2.6) in pediatrics ($n = 12$) receiving 100% meal bolus.

The percentage of time in the hyperglycemic range >250 mg/dL during HCL was 8.0 (7.5), 3.6 (3.7), 4.9 (6.3), and 6.7 (5.6) in adults with 80% meal bolus, and in adults, adolescents, and pediatrics with 100% meal bolus, respectively. The percentage of time in target range of 70 to 180 mg/dL was 69.5 (14.4), 73.0 (15.0), 72.6 (15.5), and 70.1 (12.3) in the study groups, respectively. During the overnight period, the percentage time in target range of 70 to 180 mg/dL was 87.8 (17.4), 90.8 (15.8), 84.7 (25.1), and 86.7 (17.7), respectively. Mean sensor glucose across age groups ranged from 153 (22) to 157 (20) overall and from 139 (21) to 149 (26) mg/dL during the overnight period with 100% meal bolus. Sensor glucose profiles during the open-loop and HCL phases for each study cohort are provided in Supplementary Figures S1–S4 (Supplementary Data are available at http://online.liebertpub.com/doi/suppl/10.1089/dia.2017.0346).

Percentage time in closed loop

Overall, the mean time in closed loop was 99.1% (range: 89.4%–100%). There were seven suspected infusion site

TABLE 1. CHARACTERISTICS OF THE STUDY POPULATION

Characteristic	Adults[a] (n = 24)	Adults (n = 10)	Adolescents (n = 12)	Pediatrics (n = 12)
Age, year	37.1 (14.7)	41.7 (18.1)	14.6 (1.5)	9.5 (1.7)
Female, %	67	90	50	42
Diabetes duration, year	23.0 (14.3)	23.7 (15.3)	4.6 (3.3)	4.6 (2.2)
Insulin pump use duration, year	12.8 (7.0)	12.6 (8.0)	3.2 (2.6)	3.6 (2.1)
Insulin dose open loop [U/(kg·d)][b]	0.61 (0.21)	0.53 (0.24)	0.83 (0.26)	0.79 (0.12)
Insulin dose 24-h HCL [U/(kg·d)][c]	0.60 (0.30)	0.48 (0.14)	0.83 (0.19)	0.85 (0.16)
HbA1c, %	7.7 (0.9)	7.4 (0.8)	8.2 (0.9)	7.8 (0.8)

Results are mean (standard deviation) unless otherwise indicated.
[a]Initial 24 adult subjects enrolled received 80% bolus; all subjects enrolled subsequently received 100% meal bolus.
[b]Insulin dose averaged over the 7-day open-loop phase.
[c]Insulin dose during the first 24-h HCL phase, including three meals and the overnight period.
HCL, hybrid closed loop.

TABLE 2. GLYCEMIC OUTCOMES DURING THE 7-DAY OPEN-LOOP PHASE

Parameter	Adults[a] (n=24)		Adults[b] (n=10)		Adolescents (n=12)		Pediatrics (n=12)	
	Overall	Overnight	Overall	Overnight	Overall	Overnight	Overall	Overnight
Mean sensor glucose, mg/dL	155.0 (22.6)	153.7 (35.7)	146.9 (16.4)	147.5 (18.9)	165.3 (28.3)	164.7 (32.2)	160.7 (21.1)	154.4 (21.6)
Standard deviation, mg/dL	62.7	65.8	56.3	53.3	69.4	70.7	65.5	60.9
Coefficient of variation, %	40.6	42.8	38.5	36.3	42.3	43.3	40.8	39.4
Percentage time in glucose range								
<70 mg/dL	5.2 (4.2)	7.0 (6.1)	5.4 (3.3)	4.5 (3.2)	3.5 (2.4)	3.8 (3.1)	3.2 (2.5)	3.2 (3.9)
70 to 180 mg/dL	63.8 (13.9)	62.6 (22.6)	69.0 (11.5)	69.7 (15.9)	60.0 (17.7)	60.2 (20.6)	63.5 (13.3)	67.7 (17.2)
>180 mg/dL	30.9 (15.1)	30.4 (23.0)	25.6 (11.1)	25.8 (14.9)	36.5 (18.0)	36.0 (20.2)	33.3 (14.1)	29.1 (17.3)
≥250 mg/dL	9.0 (8.1)	10.2 (13.8)	6.0 (6.5)	5.3 (6.9)	13.0 (13.5)	12.4 (14.5)	10.9 (7.8)	8.2 (8.5)

Results are sensor glucose values, mean (standard deviation) unless otherwise indicated; SI conversion factor to convert glucose to mmol/L, multiply by 0.0555. Overnight is defined as 23:00 to 07:00.

[a]Initial 24 adult subjects enrolled received 80% meal bolus; all subjects enrolled subsequently received 100% meal bolus.
[b]One additional subject completed the open-loop phase but was withdrawn by investigator as target patient enrollment of 10 subjects had been meet.

failures overall during the HCL phase and in these cases the Pods were replaced. Pod replacement for infusion site issues or temporary loss of Pod or CGM communication accounted for the interruption of closed loop.

Hypo- and hyperglycemic treatments

No serious adverse events were reported and there were no instances during the study in which the criteria were met to stop closed loop for prolonged hypo- or hyperglycemia. The overall hypoglycemia rate was 0.49 events/24 h for the study overall, 0.25 events/24 h in adults with 80% meal bolus, and 0.27, 0.83, and 0.83 events/24 h in adults, adolescents, and pediatrics with 100% meal bolus, respectively. Overall, there were 45 treatments for hypoglycemic events, 15 events in each age group, in over 2088 h of HCL use. There were 16 treatments for hyperglycemia overall with 10 (63%) events occurring in the adults receiving the 80% meal bolus.

Discussion

This multicenter, inpatient feasibility study demonstrated that the OmniPod personalized MPC algorithm performed well and was safe during day and night use over 36 h in adult, adolescent, and pediatric patients with type 1 diabetes. Positive glycemic outcomes were consistently observed across age groups that included adolescents who are typically challenged by insulin resistance and children as young as 6 years of age with enhanced insulin sensitivity.

A recent meta-analysis of 24 randomized controlled trials of closed-loop systems, including 585 patients, demonstrated that AP system use in the outpatient setting has resulted in 12% increased time in range (70–180 mg/dL) and a 50% reduction in the time spent in hypoglycemia compared to CSII with blinded CGM or SAP.[6] Based on the outcomes of this meta-analysis, current HCL systems should achieve at least 70% of sensor glucose values between 70 and 180 mg/dL with <4% of values <70 mg/dL, a CV <36%,[13] and a mean glucose of ≤155 mg/dL, equivalent to an estimated A1c of 7.0%.[14,15] The current study was able to meet all of these goals for adults, adolescents, and children, with the mean glucose within 2 mg/dL of the goal for each age group when a full meal bolus was given.

A significant benefit of AP systems in addition to overall improved glycemic control is the reduction in hypoglycemia in the overnight period.[16,17] Positive overnight outcomes were also observed in the present study with ∼85% or greater percentage time spent in the target range (70–180 mg/dL) and <0.7% time in hypoglycemia (<70 mg/dL).

Limitations of this study include its short duration and that it was conducted in a supervised research center setting, with the systems managed by healthcare providers rather than the patients. A control arm was not included as this was the first feasibility study to determine the safety of the OmniPod HCL algorithm and to further refine the algorithm before commencing longer studies in a less supervised setting with protocols, including meal and exercise challenges.

The present study was conducted using a noncommercial investigational device. The OmniPod Horizon commercial system in development is intended to be differentiated from current HCL systems with its tubeless, on-body form factor, which includes the personalized MPC algorithm embedded in the Pod and communicating directly with the latest Dexcom

TABLE 3. GLYCEMIC OUTCOMES OVER THE 36-H HYBRID CLOSED-LOOP PHASE

Parameter	Adults[a] (n = 24)	Adults (n = 10)	Adolescents (n = 12)	Pediatrics (n = 12)
Mean sensor glucose, mg/dL	161.5 (20.1)	155.0 (14.8)	153.4 (21.6)	156.9 (20.4)
Standard deviation, mg/dL	54.0	46.2	48.6	53.3
Coefficient of variation, %	33.4	29.8	31.8	34.0
Percentage time in glucose range				
<54 mg/dL	0.1 (0.3)	0.1 (0.3)	0.2 (0.3)	0.2 (0.7)
<60 mg/dL	0.2 (0.6)	0.2 (0.6)	0.7 (0.9)	0.6 (1.2)
<70 mg/dL	0.7 (1.7)	0.7 (1.2)	2.0 (2.4)	2.0 (2.6)
70 to 140 mg/dL	41.5 (18.1)	41.9 (16.3)	40.2 (15.5)	39.4 (16.1)
70 to 180 mg/dL	69.5 (14.4)	73.0 (15.0)	72.6 (15.5)	70.1 (12.3)
>180 mg/dL	29.7 (14.4)	26.3 (14.4)	25.4 (16.1)	27.9 (13.2)
≥250 mg/dL	8.0 (7.5)	3.6 (3.7)	4.9 (6.3)	6.7 (5.6)
≥300 mg/dL	2.0 (2.9)	0.5 (1.1)	0.1 (0.5)	1.0 (2.2)

Results are sensor glucose values, mean (standard deviation) unless otherwise indicated; SI conversion factor to convert glucose to mmol/L, multiply by 0.0555.
[a]Initial 24 adult subjects enrolled received 80% meal bolus; all subjects enrolled subsequently received 100% meal bolus.

TABLE 4. GLYCEMIC OUTCOMES DURING THE OVERNIGHT HYBRID CLOSED-LOOP PHASE

Parameter	Adults[a] (n = 24)	Adults (n = 10)	Adolescents (n = 12)	Pediatrics (n = 12)
Mean glucose, mg/dL	138.7 (20.3)	138.8 (21.1)	149.3 (26.4)	149.3 (24.4)
Standard deviation, mg/dL	34.7	29.9	34.6	35.2
Coefficient of variation, %	25.1	21.6	23.2	23.6
Percentage time in glucose range				
<54 mg/dL	0.0 (0.2)	0.3 (0.9)	0.0 (0.0)	0.0 (0.0)
<60 mg/dL	0.0 (0.2)	0.5 (1.5)	0.1 (0.3)	0.0 (0.0)
<70 mg/dL	0.7 (3.1)	0.7 (2.1)	0.2 (0.6)	0.1 (0.3)
70 to 140 mg/dL	64.1 (30.1)	53.8 (36.4)	43.7 (28.6)	38.7 (28.7)
70 to 180 mg/dL	87.8 (17.4)	90.8 (15.8)	84.7 (25.1)	86.7 (17.7)
>180 mg/dL	11.4 (15.6)	8.6 (16.1)	15.2 (25.3)	13.2 (17.8)
≥250 mg/dL	1.0 (4.7)	0.6 (1.9)	1.5 (4.9)	2.2 (5.8)
≥300 mg/dL	0.2 (1.1)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)

Results are sensor glucose values, mean (standard deviation) unless otherwise indicated; SI conversion factor to convert glucose to mmol/L, multiply by 0.0555. Overnight is defined as 23:00 to 07:00.
[a]Initial 24 adult subjects enrolled received 80% meal bolus; all subjects enrolled subsequently received 100% meal bolus.

CGM system. The commercial product will also include a handheld device based on smartphone hardware using an Android operating system with advanced functionality, a state-of-the-art user interface, and cloud-based data management capabilities.

Conclusions

This feasibility study demonstrated that the OmniPod personalized MPC algorithm performed well and was safe during day and night use in adult, adolescent, and pediatric patients with type 1 diabetes. Longer term studies will assess the safety and performance of the algorithm under free living conditions with extended use in patients of all ages with type 1 diabetes.

Author Disclosure Statement

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