Feasibility of Outpatient Fully Integrated Closed-Loop Control

First studies of wearable artificial pancreas

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OBJECTIVE—To evaluate the feasibility of a wearable artificial pancreas system, the Diabetes Assistant (DiAs), which uses a smart phone as a closed-loop control platform.

RESEARCH DESIGN AND METHODS—Twenty patients with type 1 diabetes were enrolled at the Universities of Padova, Montpellier, and Virginia and at Sansum Diabetes Research Institute. Each trial continued for 42 h. The United States studies were conducted entirely in outpatient setting (e.g., hotel or guest house); studies in Italy and France were hybrid hospital–hotel admissions. A continuous glucose monitoring/pump system (Dexcom Seven Plus/Omnipod) was placed on the subject and was connected to DiAs. The patient operated the system via the DiAs user interface in open-loop mode (first 14 h of study), switching to closed-loop for the remaining 28 h. Study personnel monitored remotely via 3G or WiFi connection to DiAs and were available on site for assistance.

RESULTS—The total duration of proper system communication functioning was 807.5 h (274 h in open-loop and 533.5 h in closed-loop), which represented 97.7% of the total possible time from admission to discharge. This exceeded the predetermined primary end point of 80% system functionality.

CONCLUSIONS—This study demonstrated that a contemporary smart phone is capable of running outpatient closed-loop control and introduced a prototype system (DiAs) for further investigation. Following this proof of concept, future steps should include equipping insulin pumps and sensors with wireless capabilities, as well as studies focusing on control efficacy and patient-oriented clinical outcomes.

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Automated closed-loop control of blood glucose, known as the "artificial pancreas," can have a tremendous impact on the health and lives of people with type 1 diabetes. Thus, the community of patients, families, diabetologists, and researchers have advocated strongly for the rapid commercialization of artificial pancreas technology for home use. To help facilitate this goal, the Food and Drug Administration has recently issued a guidance document to help industry and academic institutions achieve approval for outpatient evaluations of artificial pancreas technology as efficiently as possible. These studies necessarily begin in highly supervised hospital settings and progress through early feasibility, transitional, and, finally, pivotal trials, each with step-wise reduction in monitoring requirements as system performance and functionality are established under normal and stress conditions.

The components of the contemporary closed-loop control have been developed over the past 40 years, including subcutaneous insulin pump technology (1,2), continuous glucose monitoring (CGM) (3,4), and subcutaneous closed-loop control involving CGM coupled with insulin pump via a control algorithm (5–12). A comprehensive review of past and present research is presented in a recent Perspectives in Diabetes (13). However, the artificial pancreas control algorithms used by virtually all studies so far were based on laptop computers wired to a CGM and an insulin pump, a system limiting free movement and too cumbersome to be used beyond hospital confines (5–12). Nevertheless, feasibility of subcutaneous closed-loop control was demonstrated, the architecture of closed-loop control algorithms was improved, and the means for their in silico preclinical testing were introduced (14–16).

Further progress toward bringing closed-loop control to the outpatient setting depends on an artificial pancreas platform that is based on a readily available, inexpensive, wearable hardware, computationally capable of running closed-loop control algorithms, wirelessly connectable to CGM devices and insulin pumps, and capable of broadband communication for remote monitoring and safety supervision of the participants in outpatient clinical trials. A logical host for such a portable artificial pancreas platform is a contemporary smart phone, a consumer electronics device that meets virtually all of these

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aforementioned requirements. A recent report presented overnight inpatient closed-loop control in adolescents and young adults using a controller running on a Blackberry Storm smart phone (17).

In this study, we test the concept that a portable platform, the Diabetes Assistant (DiAs), running on a commercially available smart phone and fitted with a control and safety algorithms, can run closed-loop control in outpatient setting. The first pilot trials with this system were performed simultaneously in Padova and Montpellier on 26 October 2011 (18). We now present 2-day outpatient trials performed at four clinical centers. It should be emphasized that the primary goal of these trials was not a clinical outcome, but a demonstration that a contemporary smart phone is capable of running closed-loop control in outpatient setting.

RESEARCH DESIGN AND METHODS

This study combines four coordinated protocols sharing the same DiAs artificial pancreas technology conducted at the Universities of Padova (Italy) and Montpellier (France), the University of Virginia (UVA), and the Sansum Diabetes Research Institute, Santa Barbara, California. To test whether a smart phone is capable of running outpatient closed-loop control, we have configured a system comprising available components, which were linked as follows: CGM → iDex ↔ DiAs (running all closed-loop computations, user interface, and communications to peripheral devices) ↔ iDex ↔ pump. The iDex is an experimental device manufactured by Insulet (Bedford, MA), which combines a DexCom Seven Plus receiver and OmniPod insulin pump. In addition, DiAs transferred data in real time to a central location allowing remote monitoring of patient state and system functions. The primary engineering end point was the percent time with all system communications working properly; the protocol criterion for success in this early feasibility study was this time reaching >80% of the total time of investigation. Secondary end points included the estimation of the failure rates of system components, frequency analysis of lost or inaccurate CGM records, and control algorithm performance. The clinical goal was to assess patients' and clinicians' subjective impressions of the system, i.e., the feasibility of its ambulatory use, including patient usability and wearability.

Subjects

A total of 20 adults (age 21–65 years) with type 1 diabetes were studied (5 subjects at each site). Before the tests, a pilot subject was performed in Italy, France, and in the United States. All participants were experienced insulin pump users and were required to have the following: prestudy HbA_{1c} of 6–9%; predefined insulin pump parameters for basal rates, carbohydrate ratios, and insulin sensitivity factors; and proper mental status/cognition. The exclusion criteria were directed toward safety and included recent history of diabetic ketoacidosis or severe hypoglycemia, pregnancy, breastfeeding, or intention of becoming pregnant (females), uncontrolled arterial hypertension, and conditions that may increase the risk of hypoglycemia or infections.

Procedure

All protocols were approved by the review boards of the participating institutions. In addition, the United States–based studies received Food and Drug Administration approval (IDE #G120032) and the European studies received appropriate national-level certifications. All studies were registered with ClinicalTrials.gov (NCT01578980 for UVA/Sansum, NCT01447992 for Padova, and NCT01447979 for Montpellier). After consent and screening, subjects were trained to use the Omnipod insulin pump (Insulet) and participated in a 3- to 7-day pump initiation if needed. Two DexCom Seven Plus sensors (DexCom, San Diego, CA) were inserted 24–72 h before admission; throughout the trials, the sensors were calibrated per manufacturer's instructions using commercial glucometers. A calibration was performed before dinner at ~7:00 P.M., thereby allowing for further system-required calibrations to be performed during the timeframes before dinner and before breakfast. Per Food and Drug Administration recommendation, an additional (one-time) calibration was entered by the study staff if there was a discrepancy in the two sensor readings of ≥20% or if the CGM was reading <70 mg/dL and the HemoCue value was >85 mg/dL.

Participants in Italy, France, and Virginia stayed at hotels, and participants in California resided at a guest house–like outpatient research unit of the Sansum consisting of a living room, kitchen, four bedrooms, and bathrooms. The participants in the European studies were admitted individually, one subject at a time; UVA had both single and double admissions; at Sansum, all five subjects were admitted concurrently. Subjects checked in by 5:00 P.M. and met with the study team, which confirmed that the subjects had brought their insulin, pump supplies, and regular medications. The subject's pump was removed and the study pump containing the subject's insulin was started. Connections were established between DiAs and one sensor designated as primary (via the iDex), the insulin pump (via the iDex), and the remote monitoring site. The subject was then introduced to DiAs operation; the orientation took ~15–20 min to complete. The DiAs user manual (Supplementary Data) and advice from the study team were available to the subjects at all times. After this introduction, the subjects were in charge of their interactions with DiAs, controlling the system via its graphical user interface.

The protocol continued for 42 h. During the first evening/night of study, DiAs was used in open-loop mode with the subject's home insulin parameters. At 7:00 A.M. on day 2, the system was switched into closed-loop mode and remained in closed-loop control for 29 h until the subject was discharged at 12:00 P.M. on day 3. Meals were delivered to the patient's room from local restaurants or consumed at local dining facilities (e.g., dining out at a restaurant in Padova or a hotel buffet breakfast at UVA). The carbohydrate content of the meals was estimated by the subject and proper entry of the desired carbohydrate amount into DiAs was confirmed by the study physician, but there were no dietary restrictions. When the subjects were outside of their room, they were accompanied by a member of the study team and DiAs were remotely monitored continually. Figure 1 describes the timeline of the studies in Europe and in the United States.

The two protocol differences between the European (Fig. 1*A*) and United States studies (Fig. 1*B*) were as follows: in Padova and Montpellier, the patient was moved to the hospital at 7:00 A.M. on day 2 of the study for initiation of closed-loop control and remained in the hospital for 10 h before returning to the hotel for the rest of the study; in the United States studies the control algorithm was switched into "safety-only" mode for the night (11:00 P.M. to 7:00 A.M.), as requested by the Food and Drug Administration.

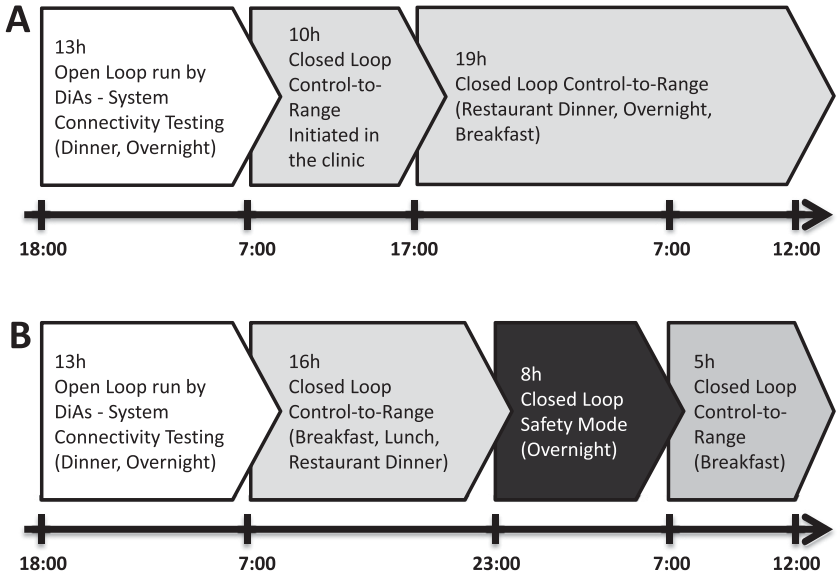

Figure 1—*Protocol design in European* (A) *and United States* (B) *investigation centers.*

Safety

A study physician, a nurse, and a technician were located in nearby rooms to provide assistance if needed. Patient data were monitored remotely via a password-protected Web site. Reference blood glucose readings were measured simultaneously by finger stick with a HemoCue (HemoCue AB, Ängelholm, Sweden) and a commercial glucometer beginning at 7:00 P.M. on the evening of admission and continuing every 2 h during the day. Overnight, there were no scheduled finger sticks; reference blood glucose measurements were taken only if DiAs or the secondary sensor alarm indicated hypoglycemia or hyperglycemia, or if the two sensors had readings diverging by >20%. Nursing staff checked DiAs and secondary CGM readings hourly overnight and system alarms were monitored remotely for the DiAs and with a baby monitor to capture alarms from the secondary CGM. Any DiAs hypoglycemia red-light warning triggered treatment with ~15 g fast-acting carbohydrate (e.g., juice), whereas hyperglycemia red-light warnings prompted checking the insulin pump for occlusion or malfunction. Any HemoCue reading >13.9 mmol/L (250 mg/dL) was followed by a β-hydroxybutyrate test (finger stick Precision Xtra β-Ketone measurement); confirmed β-hydroxybutyrate level >0.6 mmol/L was a criterion for discontinuation of the trial. In such a case, the subject could be rescheduled. Any HemoCue reading <80 mg/dL was followed-up with additional finger sticks at least every 15 min and any HemoCue blood glucose <70 mg/dL was treated with fast-acting glucose.

Technology

The hub of the DiAs system was an off-the-shelf smart phone running the Android operating system. To ensure the operation of the smart phone as a medical device, its operating system was modified to disable processes not related to closed-loop control operation and to include self-checks of system integrity. The communications between DiAs, the iDex, and the pump and the sensor were wireless, giving the patient the freedom to be fully detached from the DiAs controller. The system components worn by the patient included an Insulet OmniPod insulin pod and a DexCom Seven Plus sensor/transmitter. The patient additionally wore a pouch containing a communication box (either Viliv S5 Tablet or Galaxy Nexus phone) attached to the iDex. The iDex and the communication box were only needed for automated data transfer and pump control at this early feasibility stage. These devices did not have any computing or patient interaction functions and were abandoned in subsequent studies.

User interface

The subject controlled DiAs using graphical user interface, which allowed the following: initializing the system with the average daily insulin dose, basal rate, carbohydrate ratio, and correction factor; displaying CGM traces and insulin delivery graphs; and real-time interaction, such as entries of sensor calibrations, meal carbohydrate content, premeal capillary glucose level, and other information the subject wished to provide (e.g., exercise or hypoglycemia treatment). Two traffic-light signals presented the degree of risks for hypoglycemia or hyperglycemia as follows: green light, no risks detected; yellow light, the system is working actively to mitigate the risks by either attenuating insulin delivery if hypoglycemia is anticipated or administering correction insulin if hyperglycemia is predicted; and red light, which signifies that risks cannot be eliminated by adjustment of insulin alone and intervention is required to either consume carbohydrate or ensure that insulin is delivered properly.

Control strategy

DiAs operated in two modes, open-loop (first 13 h of each study) controlling the pump per each patient's preset basal/bolus delivery instructions and displaying CGM and insulin delivery information or closed-loop (hours 14–42 of each study) running a closed-loop control algorithm. Both modes of operation included fully automated transfer of data from the sensor to DiAs and commands from DiAs to the insulin pump. User input was required only before meals and whenever the system signaled imminent risk for hypoglycemia or hyperglycemia. The closed-loop control algorithm included two modules: *1)* safety supervision responsible for prediction of hypoglycemia, attenuation, or discontinuation of insulin delivery if hypoglycemia is anticipated and warnings if hypoglycemia is imminent and cannot be prevented by insulin discontinuation alone (19) and 2) range-correction module responsible for injecting correction boluses. The clinical use of this algorithm is described in detail in a recent publication as standard control to range (12); details on its engineering architecture also have been published (20). Occasional CGM data loss (up to 20 min) did not stop the operation of the controller; during loss of pump communication, insulin was not delivered.

Remote monitoring

In addition, DiAs transmitted data in real time through either 3G (telephone network) or WiFi to two servers (UVA and Montpellier), which allowed team members to log-in for remote observation from their locations. The server connections were one-directional: DiAs transmitted data out

but could not be controlled from a remote location for safety reasons. The transmitted data contained glucose traces, insulin infusion by the pump, and technical information about the functioning of the control algorithm but did not contain any subject identifiers; the monitoring Web sites were password-protected.

Statistical analysis

Achieving statistical significance was not an objective of this early-feasibility investigation. The data analysis corresponded to the goals of the study and included estimation of the failure rates of system components, frequency analysis of lost or inaccurate CGM records, and percent time of active system operation. Post hoc analyses included *t* test and nonparametric comparisons of open versus closed-loop parameters of glucose control observed during the study; however, the study was not powered for this outcome. Before inclusion in the analyses, CGM data were sent through retrospective recalibration using reference blood glucose readings as discussed in a recent editorial (21).

RESULTS—The focus of this investigation was on the concept of using DiAs as a smart phone–based control algorithm and user interface host. All peripheral communication devices were secondary. We assessed Dias in terms of human factors and usability, system and component performance, performance of the control algorithm, utility of remote monitoring, and clinical events.

Human factors and usability

Before this study, a formative evaluation of the DiAs user interface was conducted to evaluate the feasibility of the design for patient use. Heuristic evaluation (expert review) was followed by three focus groups with type 1 diabetic patients with varying exposure to diabetes technology (n = 13). Feedback was gathered on various system components addressing user interaction, system features, and capabilities. Change recommendations were prioritized, and users were asked to rate the system on several criteria. Users indicated the importance of maintaining all existing insulin pump and CGM device functionalities (22).

The DiAs graphical user interface (Supplementary Data) proved to be reliable and well-understood by the subjects. All were able to easily navigate through the graphical user interface commands on their own in both open-loop and closed-loop modes of operation, view CGM and insulin information, and administer meal or correction boluses as needed. The subjects were free to move around the facility and in its vicinity. One subject used a hotel treadmill, one subject in Italy rode a bike, one subject in France walked to nearby museums, and five subjects took a shower with the pouch hanging just outside of the shower. Subjects also were free to entertain family and friends in their individual quarters.

System wearability was evaluated in relative terms, comparing DiAs to previous laptop-based systems. With the transition to a smart phone as a system hub and to wireless data transmission, the weight of a closed-loop control system was reduced several-fold. Figure 2*A* presents photos of DiAs displaying CGM and insulin delivery traces and the entire system worn by a study subject. DiAs communicated wirelessly with the iDex/communication box; these devices are placed in a pouch on the patient's belt. The iDex communicated wirelessly to an OmniPod insulin pump and to a DexCom sensor visible as attached on the subject. The communication range of the iDex with the insulin pod and DexCom sensor was ~5 inches, which necessitated the use of a belt pouch. With this set-up, the subjects were able to maintain activities of daily living, a necessary first step toward routine outpatient use.

System and component performance

Table 1 presents metrics of the technical performance of the artificial pancreas system overall and during the open-loop and closed-loop portions of the study. Two subjects described developed hyperglycemia with ketones because of pump site or pod failures in the initial open-loop portion of the study and were rescheduled. Only the completed second study data for the rescheduled subjects are included in this analysis. Additionally, the three pilot subjects for each country were not included in the analysis; the data of the first two from Italy and France were recently published (18). Overall, the artificial pancreas system was functional 98% of the time, which exceeded the initially set primary end point goal of 80%.

One element of system connectivity should be noted. In the European studies and in the first United States–based studies we used a Viliv S5 tablet to communicate with the iDex, which was then replaced by a more reliable Samsung Galaxy Nexus smart phone. As evident from Table 1, this replacement had a substantial effect on system reliability, reducing almost five-fold the number of unplanned system restarts because of loss of signal transmission. Because the communication box was dedicated solely to data transmission, its replacement did not affect the conceptual or the computing outcomes of the study.

Further, Table 1 presents data on the performance of the principal system components: the CGM, DiAs, and the insulin pump. Of particular importance for fully integrated closed-loop control is the stability of interdevice connections (sensor → iDex ↔ smart phone ↔ iDex ↔ insulin pump). Table 1 presents the availability of CGM and insulin pump communications with DiAs during the study.

Performance of the control algorithm

Although the study was not designed to test algorithm performance or to compare open-loop versus closed-loop, Table 2 presents a set of glycemic control metrics and certain post hoc comparisons of open-loop versus closed-loop nights using retrospectively recalibrated CGM data (21). The outpatient performance of the controller was similar to its inpatient performance of this same control algorithm observed in a previous study (standard control to range, 12); thus, first indications are that a different platform (e.g., a smart phone) under different outpatient conditions may achieve similar performance as a laptop-based system in the hospital. On open-loop versus closed-loop control, we observed 80 vs.72% time within target range (P = 0.22) and 0.53 vs. 0.27 hypoglycemic episodes ≤3.9 mmol/L (70 mg/dL) per 24 h (P = 0.16); in other words, there were no significant differences between open-loop and closed-loop control overnight, which is an expected result for standard control to range (12).

Utility of remote monitoring

Figure 2*B* presents a screenshot of the remote monitoring system operation during the study at Sansum. Each of the five subjects participating simultaneously in this study is represented by an icon on the computer screen. The icon summarizes real-time information, including patient identification number, current CGM reading and direction of change, the state of the hypoglycemia and hyperglycemia alerts, and a message informing the technician of possible risks or system malfunction. Safety supervision module was active for three patients (identification numbers 211, 212, and 214) as indicated

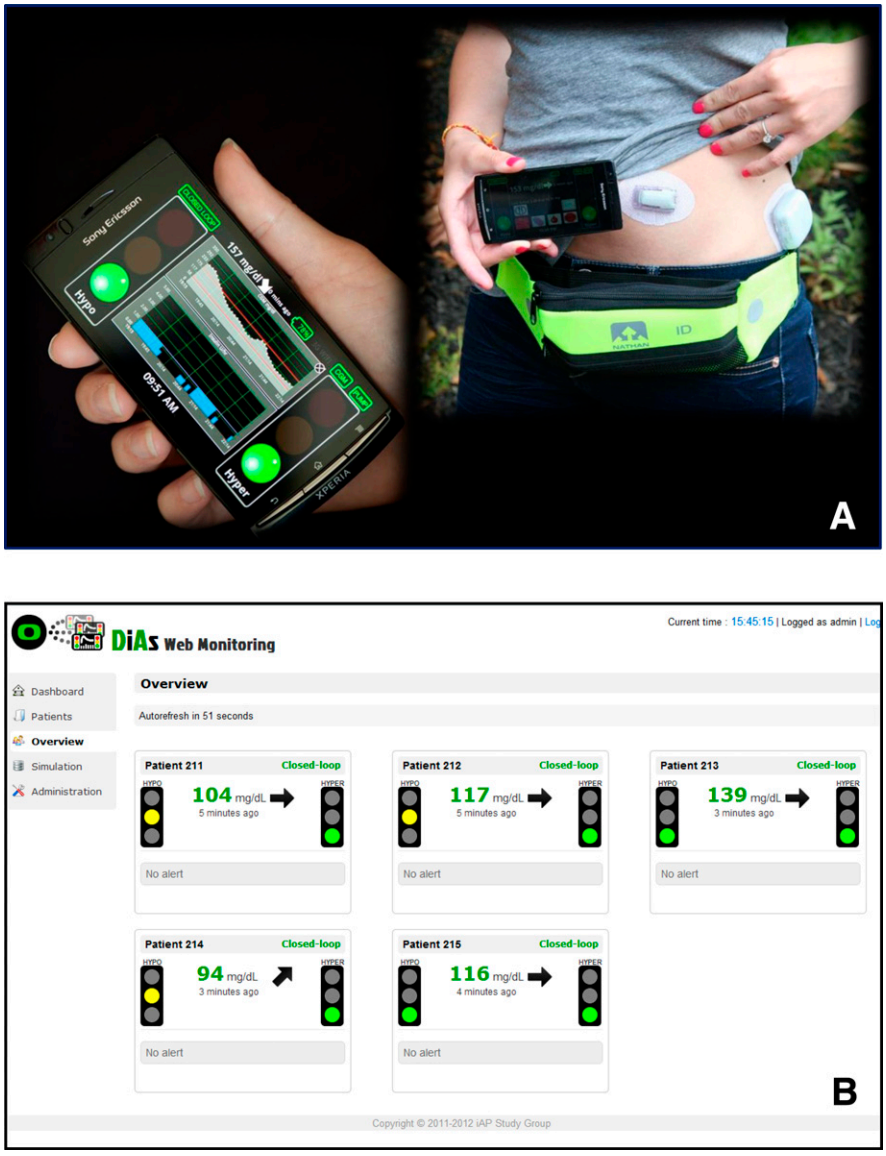

Figure 2—A: *Photos of the DiAs smart phone displaying CGM and insulin delivery traces* (left) *and the entire system worn by a study subject* (right). B: *Screenshot of the remote monitoring system operation during the trials at Sansum. Each of the five subjects participating simultaneously in these trials is represented by an icon on the computer screen. HYPER, hyperglycemia; HYPO, hypoglycemia.*

by yellow hypoglycemia lights. There were no error messages. Each icon can be clicked during a monitoring session, which will display more detailed information for this subject, including detailed records of insulin delivery, glucose data, and the algorithm functions. Throughout the study, observation of the participants was performed mainly through the remote monitoring system, which proved to be a useful tool.

Clinical events

On six occasions during the study (two during open-loop and four during closed-loop control), carbohydrate treatment was administered for blood glucose levels <3.3 mmol/L (60 mg/dL), for a total of 0.17 events per 24 h of system operation.

There were no instances of patient-initiated system shutdown, but the trials were discontinued by study staff on three occasions. The first two events occurred early, before initiation of closed-loop control, and the subjects were rescheduled for subsequent admissions, which concluded successfully. The third subject was discontinued at study hour 36 and was not rescheduled. Subject 1 experienced hyperglycemia of 260 mg/dL with β-hydroxybutyrate level of 0.7 mmol/L 2 h after the insulin pump was initiated (consistent with pod compared with insertion site failure). Subject 2 dropped the communication tablet and attempts to restart it were unsuccessful. After the connection was reestablished with a new tablet, the insulin pod alarmed, prompting a pod change. The new pod occluded (blood noted in pod tubing), resulting in β-hydroxybutyrate of 1.3 mmol/L. Subject 3 experienced hyperglycemia to 295 mg/dL with β-hydroxybutyrate of 0.7 mmol/L at hour 36 of the study. At that time, DiAs was running in safety mode (Fig. 1) with the range controller switched off, delivering only basal rate (4.1 units in the previous 6 h). The subject's CGM glucose was noted to increase from 180 mg/dL to 295 mg/dL over the final 2 h, suggesting that a pod occlusion (unconfirmed) may have contributed to this event. These three patients were treated with subcutaneous insulin, resulting in prompt resolution of the mild ketosis.

CONCLUSIONS—Technology advancements in the past year made possible the development of DiAs, wearable ambulatory artificial pancreas platforms using an off-the-shelf smart phone as a computational hub. Besides more user-friendly touch-screen interface and wireless connectivity, one easily quantifiable result of the transition from a laptop-based to a phone-based closed-loop control is a significant reduction in the system weight, which brings the system one important step closer to ambulatory use. Ultimately, this would lead to "closing the loop" with a portable minimally invasive system suitable for home use. Industry is currently transitioning CGMs and pumps to include wireless connectivity; thus, DiAs is only the first of many portable devices that will be capable of wireless data exchange and fully integrated closed-loop control.

At the time of this outpatient trial, the DexCom Seven Plus and the OmniPod Insulet pump had short-range wireless capability to communicate with an iDex research platform. Also, for the iDex to establish wireless communication with DiAs, an intermediary tablet (or a cell phone) needed to be connected to the iDex. Hence, there was short-range wireless communication from the patient (wearing a pod and sensor/transmitter) to a pouch containing the iDex and tablet (or cell phone), and long-range wireless

Table 1—*Performance metrics for the functioning of the artificial pancreas system used in these studies and of its primary components*

		Open-loop control	Closed-loop control	Combined
Overall system performance		274/277 h	533.5/549.5 h	807.5/826.5 h
Primary end point: Total duration of accurate DiAs communication functioning/total possible system time from patient admission to discharge and time of proper communication function		98.9%	97.1%	97.7%
Frequency of unplanned system resets or restarts, events/total time and events/24 h of DiAs operation	Viliv S5 tablet	25/167 h 3.59	35/331.5 h 2.53	60/498.5 h 2.89
	Galaxy Nexus phone	1/110 h 0.22	7/218 h 0.77	8/328 h 0.58
CGM and CGM–DiAs communication				
Reliability of CGM, number of nominal CGM cycles during study period for which the primary CGM was reporting data and percent of total		2,692/3,082 87.3%	6,107/6,598 92.6%	8,799/9,680 90.9%
Frequency of CGM malfunction necessitating sensor replacement, events/total time and events/24 h of operation		0/277 h 0.00	1/549.5 h 0.04	1/826.5 h 0.03
Frequency of sensor calibrations that were requested by the CGM, events/total time and events/24 h of operation		20/277 h 1.73	7/549.5 h 0.31	27/826.5 h 0.78
Frequency of sensor calibrations that were forced by the user, events/total time and events/24 h of operation		29/277 h 2.51	57/549.5 h 2.49	86/826.5 h 2.50
Reliability of CGM–DiAs communication, number and percent of total CGM cycles with values reported by the CGM and received by DiAs			6,010/6,107 98.4%	
DiAs platform				
Reliability of control algorithm, percent closed-loop control cycles in which control algorithm produced dosing recommendations, provided that CGM values were available in the past 20 min			100%	
Frequency of DiAs malfunction necessitating replacement of the smart phone platform, events/total time and events/24 h of operation		2/277 h 0.17	1/549.5 h 0.04	3/826.5 h 0.09
Insulin pump				
Reliability of insulin pump components (pump occlusions or iDex malfunction leading to pod replacement), events/total time and events/24 h		2/277 h 0.17	2/549.5 h 0.09	4/826.5 h 0.12
Reliability of DiAs insulin pump communication, number of microboluses delivered/expected per algorithm recommendation during open-loop and closed-loop	Viliv S5 tablet	1,679/2,121 79.2%	3,268/3,576 91.4%	4,947/5,697 86.8%
	Galaxy Nexus phone	1,226/1,279 95.9%	2,684/2,771 96.9%	3,910/4,050 96.5%

Data presented separately for the two communication boxes used throughout the study.

communication between the pouch and the DiAs artificial pancreas platform. These intermediate devices are now being phased out; communication boxes are no longer necessary. Such a technology improvement was anticipated in our study; thus, we focused on the smart phone computing and user-interface capabilities of the DiAs, assuming that this would be the device that is here to stay.

Special emphasis should be placed on the fact that the subjects were operating the system by themselves most of the time. To the best of our knowledge, this is the first trial in which the subjects were responsible for the oversight of their closed-loop systems, a step that is critical for outpatient deployment of closed-loop control. Based on this feedback, we conclude that the form factor of DiAs as an artificial pancreas platform is appropriate for outpatient use. However, before long-term efficacy studies comparing outpatient artificial pancreas with

Table 2—*Performance of the control algorithm*

	Open-loop control	Closed-loop control	Combined
Time within the target range of 3.9–10 mmol/L (70–180 mg/dL) during the day (7:00 A.M. to 11:00 P.M.)		68%	
Time below the target of 3.9 mmol/L (70 mg/dL) during the day (7:00 A.M. to 11:00 P.M.)		1.74%	
Time within the target range of 3.9–10 mmol/L (70–180 mg/dL) overnight (11:00 P.M. to 7:00 A.M.)	80%	72%	75%
Number of hypoglycemic episodes below the target of 3.9 mmol/L (70 mg/dL) overnight (11:00 P.M. to 7:00 A.M.), events/24 h	0.53	0.27	0.36
Time below the target of 3.9 mmol/L (70 mg/dL) overnight (11:00 P.M. to 7:00 a.m.)	1.6%	0.69%	0.99%

sensor-augmented pump therapy can proceed, system wearability during daily living and the reliability of device communications must be ensured. Testing of the system at four different sites in three countries and in a variety of hotel and restaurant settings using one, two, or five systems concurrently provided an opportunity to challenge DiAs with multiple scenarios that are likely to be encountered in nonhospital and, ultimately, home settings.

In general, the technical performance of the DiAs system with overall operational time of 98% exceeded the set goal of 80%. In retrospect, this goal may have been conservative, but before this study it was generally unclear whether a smart phone can run closed-loop control, and there was no experience to guide the choice of this goal. The principal system components—sensor, DiAs, and insulin pump—were reasonably reliable, with 0.03, 0.09, and 0.12 malfunction events necessitating device replacement per 24 h, respectively. Occasional CGM data points were lost (8.1%), but this did not result in skipping control cycles or discontinuation of the study; by design, control to range would function during transient absence of CGM data because the controller intervenes only if risks for hypoglycemia or hyperglycemia are detected (20).

Finally, we must emphasize the utility of remote monitoring, which was available on site and at remote locations (i.e., studies in Europe or in California were observed from Virginia and vice versa in real time). This was a critical aspect for patient safety that allowed close supervision so that intervention could occur quickly if needed. Our system allowed monitoring concurrently multiple patients, a feature that was tested at Sansum with five patients simultaneously. This feature alone will allow acceleration of the number of subjects who could be studied at the same time, reducing staffing costs and making artificial pancreas research more efficient.

In summary, a wearable inexpensive closed-loop control platform (DiAs) was created and tested in early feasibility studies. Combined with real-time remote monitoring, this system opens the possibility for large pivotal trials that will establish the artificial pancreas as a viable mainstream treatment strategy in type 1 diabetes.

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B.P.K. designed the study protocol, contributed to the technology design and to the clinical execution of the study, co-wrote the manuscript, and was the principal investigator of the project. E.R. was the principal investigator at the Montpellier site, co-designed the study protocol, contributed to the study approval and the clinical execution, and co-wrote the manuscript. C.C. co-designed the study protocol, contributed to the technology design and to the clinical execution of the study, co-wrote the manuscript, and was the principal investigator for the Italian studies. H.C.Z. co-developed the study protocol, directed the clinical trials in California, and co-wrote the manuscript. P.K.-H. was the chief engineer of the system used in the study responsible for all technical aspects of the outpatient artificial pancreas functioning. S.M.A. co-wrote the study protocol, was the study physician overseeing the execution of the clinical studies in Virginia, interpreted data, and co-wrote the manuscript. S.A.B. was the study physician responsible for the execution of the clinical studies in Virginia, interpreted data, and co-wrote the manuscript. D.R.C. coordinated all clinical aspects of the project design and execution, including on-site project management at University of Virginia and Sansum. M.D.B. co-designed the control algorithm and analyzed the data from this project. A.Fa. contributed to the clinical execution of the study and reviewed the manuscript. M.-J.P. contributed to the clinical execution of the study. J.P. was the primary designer of the remote monitoring system and was responsible for the technical execution of the study in France. D.B. was the study physician responsible for the execution of the clinical studies in Padova, interpreted data, and edited the manuscript. S.D.F. was responsible for technical aspects of the system functioning during the clinical studies in Padova, was involved in the testing phase of the system, and interpreted and processed data. R.V. (Padova) was co-responsible for technology oversight during the clinical trials in Padova and processed the data from Italy. A.Fi. was co-responsible for the execution of the clinical studies in Padova. R.S. was co-responsible for the execution of the clinical studies in Padova. A.A. directed the medical team in Padova and edited and revised the manuscript. F.J.D. was the principal investigator of the project in California and edited and revised the manuscript. B.P.K. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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