Supplementary Material

The pAPS system functionality

The portable Artificial Pancreas System (pAPS)[1] (**Figure 1**) is a research platform that facilitates the evaluation of novel closed-loop algorithms . In brief, the system includes a continuous glucose monitoring system (CGM G4 Professional, Dexcom, San Diego CA), an Omnipod pump (Insulet Corporation, Acton MA) and a tablet computer (Dell Venue™ 10 Pro, Dell Technologies, Round Rock, TX) that centrally manages all the devices. Sensor glucose values are transmitted every 5 minutes to the CGM receiver that is serially connected to the tablet. The transmitted glucose value is used by the hypoglycemia detection and mitigation algorithm to predict impending hypoglycemia and to calculate the dose of study drug; a signal is delivered from the tablet to the pump relay via Bluetooth Low Energy (BLE) communication for fully automated delivery of study drug The pAPS can notify the clinical team by means of visual and audible alarms in the tablet and can send wirelessly a short message service (SMS) and multimedia message service (MMS) to their personal cellphones. The user can interact with the system (e.g. set subject parameters, initiate or terminate the session) through a touch graphical user interface implemented on the tablet.

The pAPS system has reliably supported many inpatient and outpatient clinical studies [2-5] that used distinct internal algorithms. The system using the PBH-specific hypoglycemia detection and mitigation algorithm was previously described [6]. In that feasibility study, the intervention of the clinical team was required to activate the pump to deliver the dose suggested by the algorithm; by contrast, in the current study the system runs uninterrupted in closed-loop during the study session. The development and the fine tuning of the internal algorithm is described in detail in Laguna et al.[6]. Compared to the original version of the algorithm[6], some technical aspects, including how to best handle missing CGM values in case of lost connectivity or CGM malfunction, have been optimized. The key functionalities of the algorithm are summarized below.

The hypoglycemia detection and mitigation algorithm consists of two main modules that are executed concurrently to ensure timely delivery of the study drug. The first module is the PBH detection algorithm that was specifically tailored to prevent postprandial hypoglycemia as observed in PBH. The PBH detection algorithm utilizes a meal detection algorithm to determine if a meal has been consumed, based on the history of glucose rate of change. Three distinct modes of operation are specified: “waiting for meal”, “waiting for peak” and “waiting for hypoglycemia.”. The PBH algorithm will command the delivery of the drug dose and will issue a PBH alarm, notifying the clinical team of impeding hypoglycemia, if a series of logical statements are satisfied: (1) the operating mode “waiting for

hypoglycemia" (indicating the post-meal state) is active. (2) current sensor glucose values less than a threshold of 150 mg/dL, (3) the glucose rate of change to be negative and between -5 mg/dL/min and -0.5 mg/dL/min, indicating that glucose levels are falling rapidly, (4) the estimated time to fall below the hypoglycemic threshold (75 mg/dL) to be <30 min

The second module of the algorithm is the low glucose prediction (LGP) algorithm[7]. The modified LGP module can be activated irrespectively of the operating mode, which means that it can support participants in case of rebound hypoglycemia or hypoglycemic episodes that may not be associated with a meal. The execution of the LGP algorithm will also trigger the delivery of study drug and will issue an LGP alarm. This can occur in two cases: The first case includes that 1) the current sensor glucose is less than 100 mg/dL, 2) there is a rapid drop of glucose levels (rate of change between -5 mg/dL/min and -0.55 mg/dL/min) and 3) the time to hypoglycemia state is predicted to be less than 20 minutes. The second case can occur when CGM is less than 75 mg/dL and glucose is dropping at a rate less than 0.1 mg/dL/min.

To prevent the issuing of consecutive alarms and study drug deliveries, and to allow time for study drug metabolic efficacy, the PBH and LGP algorithms are supported by a drug delivery management algorithm. This algorithm ensures that during a postprandial period (i.e. a meal has been detected) only two doses of study drug may be administered, the first dose being 300 μg. If the system predicts or detects a second hypoglycemic event, a second dose of either300 μg or 150 μg of study drug is delivered, based on filtered glucose levels below or above 75 mg/dL, respectively. Additionally, the system will not proceed with any deliveries or alarms for 30 minutes after a dose has been delivered. This lockout period is reduced to 15 minutes if severe hypoglycemia is detected (sensor glucose < 65 mg/dL). The functionality of the algorithm is illustrated in Supplemental Figure 5.

Supplemental Figures:

Supplemental Figure 1. Study Design: Visits 1 and 2 could be combined if study investigators deemed high likelihood that potential participants would meet eligibility criteria. Visit 4 CGM insertion could be performed at home the participant had sufficient proficiency. CGM, continuous glucose monitor; hrs, hours.

Supplemental Figure 2. Glucose Levels: Representative plot of plasma glucose levels of one participant (same as representative participant from Figure 2) who completed study visits receiving either vehicle (blue) or glucagon (red). During the vehicle delivery visit the participant received two infusions before reaching clinically significant hypoglycemia, at which time intravenous dextrose was administered and the closed-loop system was discontinued. During the glucagon treatment visit the participant received two infusions and clinically significant hypoglycemia was prevented.

Supplemental Figure 3. Local Pain Scores: Pain scores at the site of drug infusion with initial drug delivery, indicated for individual patients; lines illustrate mean and SEM. Pain was typically transient, lasting only for the period of infusion (< 5 minutes). For first study drug delivery, paired p=0.87 for vehicle vs. glucagon. (A second dose was not consistently delivered, so paired analysis was not possible.)

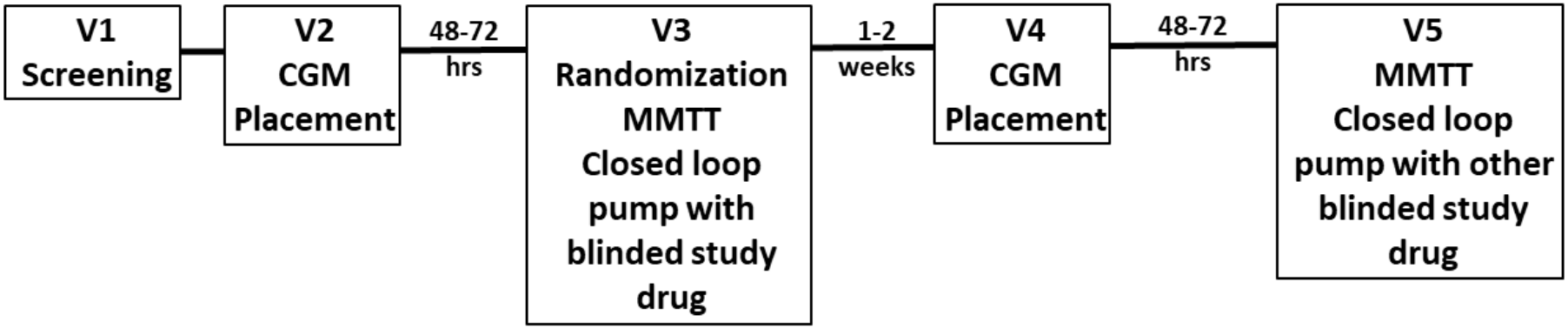
Supplemental Figure 4. Draize Scores: Skin at the site of patch pump and study drug infusion was examined and scored for erythema and edema using the Draize scale at 30 minutes after pump removal and at the end of the study visit.

Supplemental Figure 5. Plot of APS responses from a representative study visit when vehicle was delivered. A. Filtered CGM values (blue dots), rate of change (green dashed line) and filtered rate of change (yellow dashed line). Values must be within the shaded area in order to trigger an alarm. Filtered CGM values must be less than the PBH threshold (dashed blue horizontal line) in order to trigger a PBH alarm. Alternatively, if the filtered CGM values are less than the hypoglycemia threshold (dashed light blue horizontal line) an LGP alarm can be triggered After a meal is detected (cyan triangle) the PBH algorithm is enabled and can be active for a time window (indicated by a black vertical dashed line). In this example, a second active PBH period occurred due to the glucose peak around 13:45. B. Calculated time to exceed the hypoglycemic threshold. Negative values illustrate filtered CGM values being less than the hypoglycemic threshold. C. Deliveries of study drug (black lines, vehicle for this visit),

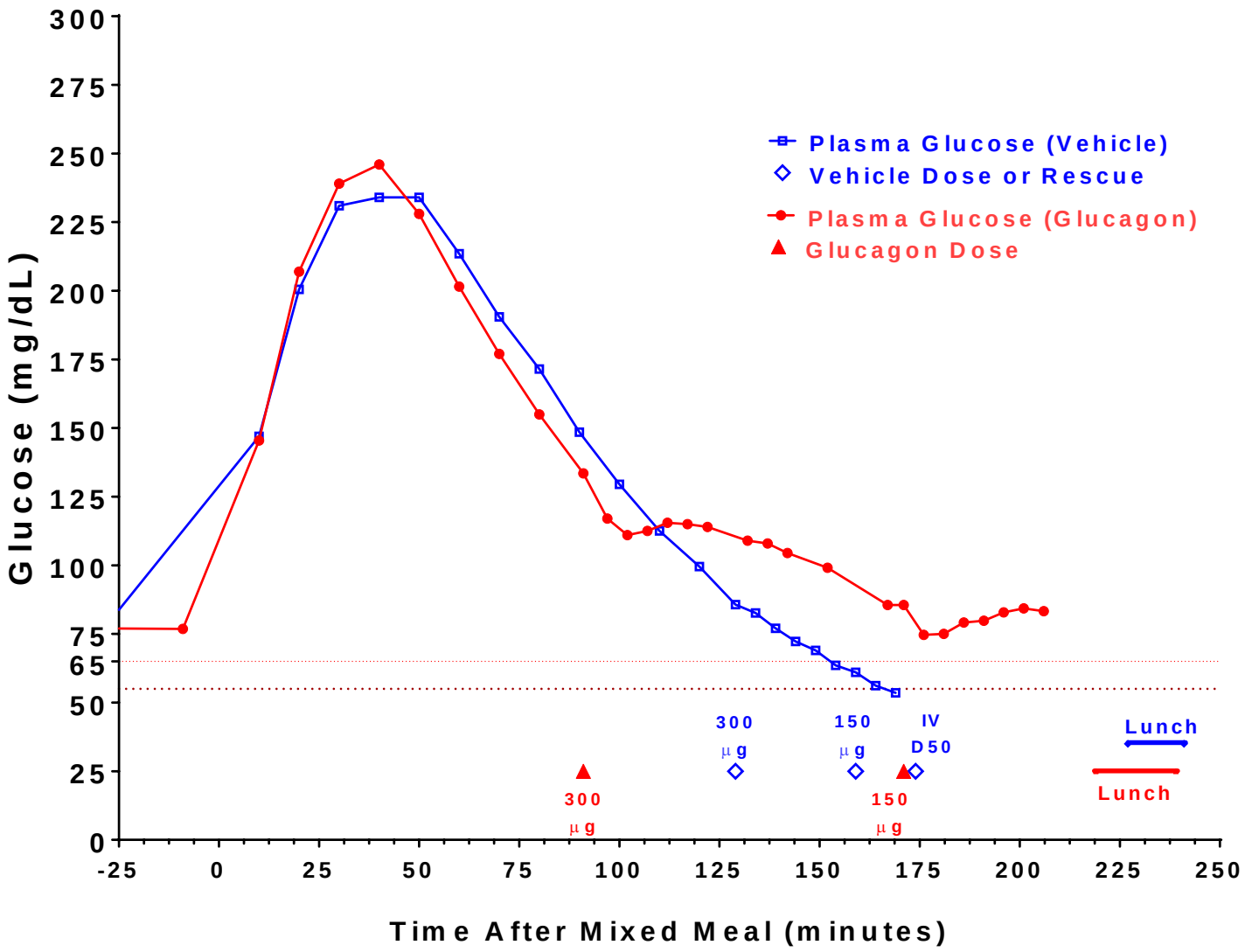
which in this example The PBH and LGP alarms are shown in different colors. The lockout periods after the drug delivery are shown in shaded grey.

Supplemental Table 1. (A) Glucagon, (B) insulin, and (C) C-peptide levels, measured at baseline, at specified time points after mixed meal ingestion, at the time of 1st and 2nd hypoglycemia mitigation alerts and at specified intervals after alert and study drug infusions.

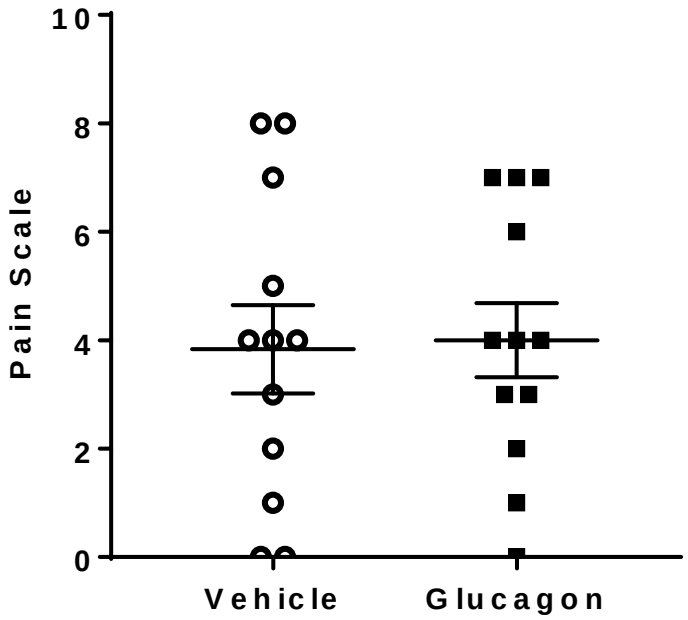
Supplemental Figure 1. Study Design



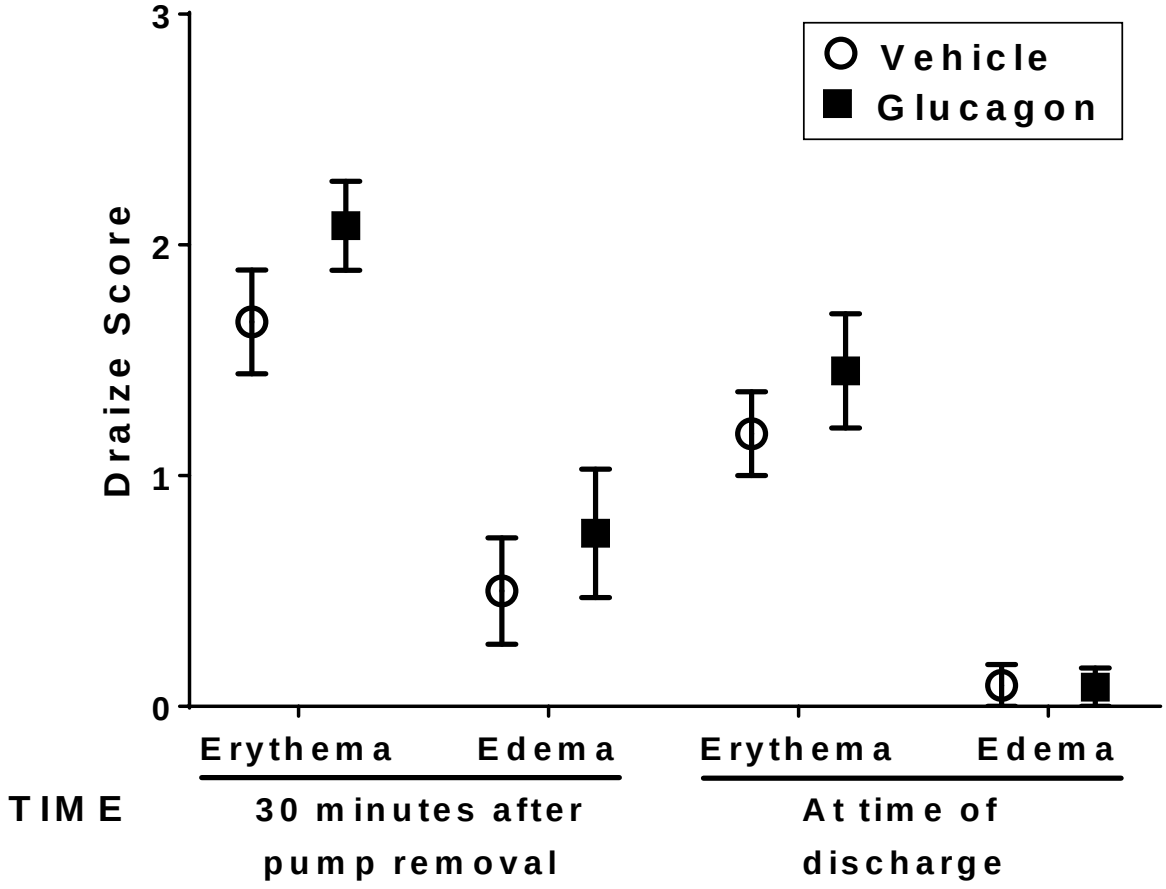
Supplemental Figure 2. Glucose Levels



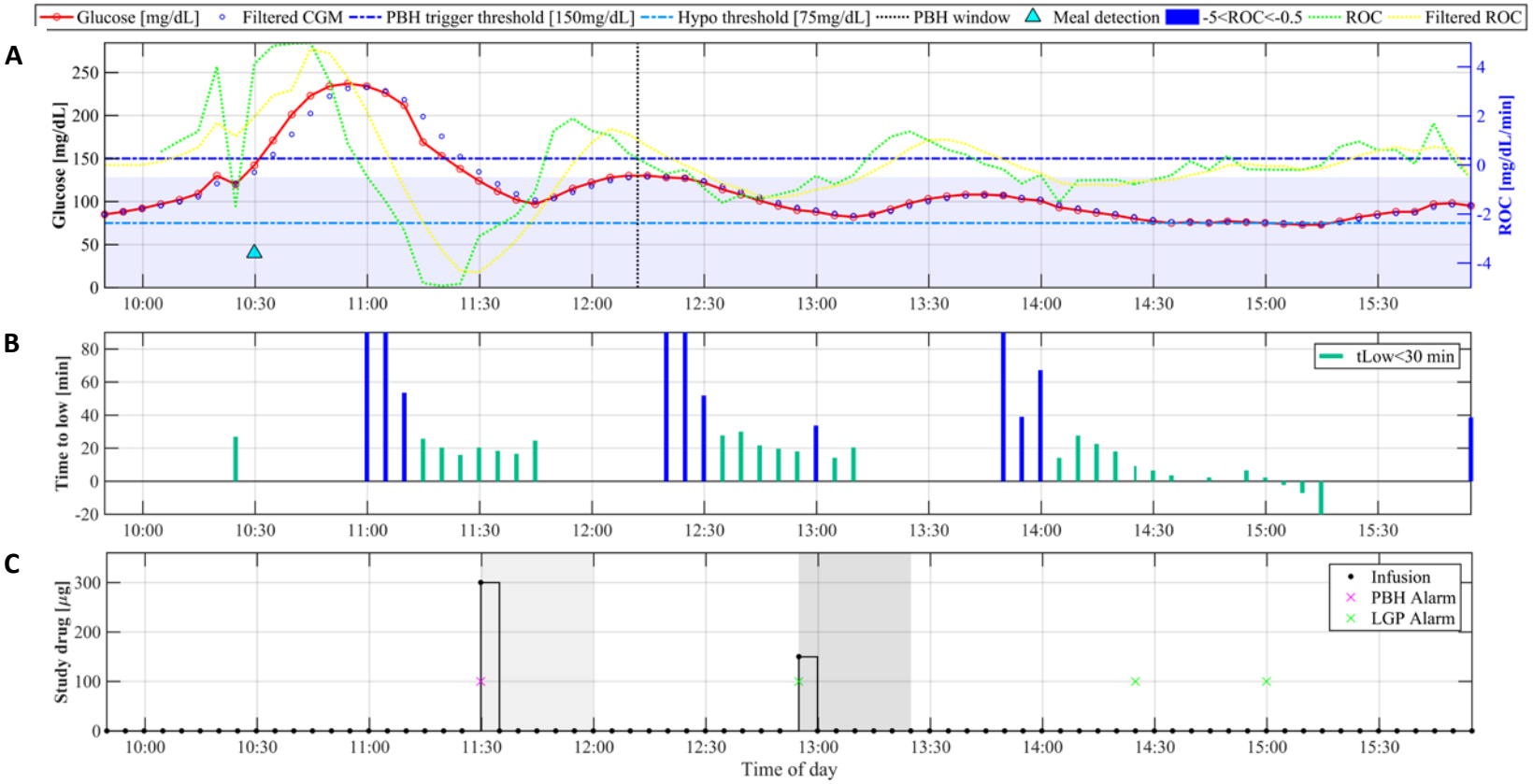
Supplemental Figure 3. Local Pain Scores



Supplemental Figure 4. Draize Scores



Supplemental Figure 5. Plot of APS responses from a representative study visit when vehicle was delivered



Supplemental Table 1A. Glucagon Levels

	Vehicle Delivery				Glucagon Treatment				Vehicle vs Glucagon
Timepoint	**mean (pg/mL)**	**SEM**	**n**	**vs Baseline p**	**mean (pg/mL)**	**SEM**	**n**	**vs Baseline p**	**p**
Baseline	20.8	2.3	12	-	34.4	7.0	12	-	0.889
30 min	28.8	2.5	12	0.935	72.4	8.4	12	0.699	0.657
60 min	11.7	0.9	12	0.926	21.4	3.1	12	0.894	0.921
120 min	10.0	0.0	1	0.853	14.4	4.4	2	0.978	0.826
Alarm 1	12.5	1.3	12	0.993	16.7	2.3	12	0.856	0.974
10 min	13.5	1.0	12	0.941	417	90.8	12	<0.001	<0.001
20 min	16.0	1.4	12	0.961	1168	218	12	<0.001	<0.001
30 min	19.2	3.3	6	0.954	1231	187	11	<0.001	<0.001
60 min	-	-	0	-	756	50.9	11	<0.001	-
Alarm 2	22.7	4.1	9	0.861	465	101	5	0.005	0.004
20 min	25.1	4.3	6	0.983	823	131	5	<0.001	<0.001
30 min	25.2	4.7	6	0.984	758	106	5	<0.001	<0.001

Supplemental Table 1B. Insulin Levels

Timepoint	Vehicle Delivery				Glucagon Treatment				Vehicle vs Glucagon
	mean (µU/mL)	SEM	n	vs Baseline p	mean (µU/mL)	SEM	n	vs Baseline p	p
Baseline	4.77	0.66	12		4.26	0.52	12		0.950
30 min	243	27.8	12	<0.001	327	46.3	12	<0.001	0.092
60 min	340	70.5	12	<0.001	371	87.7	10	<0.001	0.510
120 min	30.7	0.00	1	0.767	22.1	12.1	2	0.469	0.877
Alarm 1	101	26.1	12	0.066	154	78.3	12	0.007	0.371
30 min	22.0	6.21	6	0.936	122	66.0	11	0.033	0.093
60 min	-	-	-	-	48.4	16.9	11	0.404	-
Alarm 2	17.9	3.28	8	0.910	36.8	14.6	5	0.918	0.888
30 min	8.80	1.18	5	0.930	21.5	6.53	5	0.740	0.757

Supplemental Table 1C. C-peptide Levels

Timepoint	Vehcile Delivery				Glucagon Treatment				Vehicle vs Glucagon
	mean (µU/mL)	SEM	n	vs Baseline p	mean (µU/mL)	SEM	n	vs Baseline p	p
Baseline	4.77	0.66	12		4.26	0.52	12		0.950
30 min	243	27.8	12	<0.001	327	46.3	12	<0.001	0.092
60 min	340	70.5	12	<0.001	371	87.7	10	<0.001	0.510
120 min	30.7	0.00	1	0.767	22.1	12.1	2	0.469	0.877
Alarm 1	101	26.1	12	0.066	154	78.3	12	0.007	0.371
30 min	22.0	6.21	6	0.936	122	66.0	11	0.033	0.093
60 min	-	-	-	-	48.4	16.9	11	0.404	-
Alarm 2	17.9	3.28	8	0.910	36.8	14.6	5	0.918	0.888
30 min	8.80	1.18	5	0.930	21.5	6.53	5	0.740	0.757

Supplement References:

1. Dassau E, Zisser H, C Palerm C, A Buckingham B, Jovanovic L, J Doyle F. Modular artificial beta-cell system: a prototype for clinical research. *J Diabetes Sci Technol* 2008; **2**(5): 863-72.
2. Pinsker JE, Lee JB, Dassau E, et al. Randomized Crossover Comparison of Personalized MPC and PID Control Algorithms for the Artificial Pancreas. *Diabetes Care* 2016; **39**(7): 1135-42.
3. Dassau E, Brown SA, Basu A, et al. Adjustment of Open-Loop Settings to Improve Closed-Loop Results in Type 1 Diabetes: A Multicenter Randomized Trial. *J Clin Endocrinol Metab* 2015; **100**(10): 3878-86.
4. Buckingham BA, Christiansen MP, Forlenza GP, et al. Performance of the Omnipod Personalized Model Predictive Control Algorithm with Meal Bolus Challenges in Adults with Type 1 Diabetes. *Diabetes Technol Ther* 2018; **20**(9): 585-95.
5. Pinsker JE, Laguna Sanz AJ, Lee JB, et al. Evaluation of an Artificial Pancreas with Enhanced Model Predictive Control and a Glucose Prediction Trust Index with Unannounced Exercise. *Diabetes Technol Ther* 2018; **20**(7): 455-64.
6. Laguna Sanz AJ, Mulla CM, Fowler KM, et al. Design and Clinical Evaluation of a Novel Low-Glucose Prediction Algorithm with Mini-Dose Stable Glucagon Delivery in Post-Bariatric Hypoglycemia. *Diabetes Technol Ther* 2018; **20**(2): 127-39.
7. Harvey RA, Dassau E, Zisser H, Seborg DE, Jovanovič L, Doyle FJ. Design of the health monitoring system for the artificial pancreas: low glucose prediction module. *J Diabetes Sci Technol* 2012; **6**(6): 1345-54.