

SUPPLEMENTARY MATERIAL

Improvements in Glycemic Control Achieved by Altering the $t_{\max}$ Setting in the iLet[®] Bionic Pancreas When Using Fast-Acting Insulin Aspart: A Randomized Trial

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Participant randomization

All participants received a unique ascending-order randomization number at the trial site, which encoded the participant's assignment to one of the treatment sequences according to the randomization schedule. A randomization schedule was generated before the trial. All participants were assigned a unique randomization number in ascending order at the trial site. The randomization number encoded the participant's assignment to one of the treatment sequences of the trial, according to the randomization schedule. Blocking was used, with two blocks of four participants within each cohort.

Inclusion criteria to those presented in the manuscript:

- Aged 18–75 years
- Diagnosed with type 1 diabetes at least 12 months prior to the day of screening
- Glycated hemoglobin (A1C) ≥ 6.5 – $\leq 9.0\%$ (≥ 47 – ≤ 75 mmol/mol) at screening

- Treated with continuous subcutaneous insulin infusion (CSII) for at least 12 months prior to the day of screening
- Informed consent was obtained before any trial-related activities. Trial-related activities are any procedures carried out as part of the trial, including activities to determine suitability for the trial
- Have a mean total daily dose of insulin ≥ 20 units
- Familiar with continuous glucose monitoring, as judged by the investigator
- Has someone over 18 years of age who
 1. Lives with them
 2. Has access to where they sleep
 3. Is willing to be in the house when the participant is sleeping, and
 4. Is willing to receive calls from the study staff and check the welfare of the study participant
- Body mass index ≤ 35.0 kg/m² at screening
- Able and willing to remain in a designated place for the specified duration of the 'in-patient' periods
- Lives within a 120-min drive from the central monitoring location (site)

Exclusion criteria

- Known or suspected hypersensitivity to trial product(s) or related products
- Previous participation in this trial, defined as signed informed consent

- Female who is pregnant, breastfeeding, or intends to become pregnant or is of child-bearing potential and not using an adequate contraceptive method (adequate contraceptive measures as required by local regulation or practice)
- Participation in any clinical trial of an approved or non-approved investigational medicinal product within 30 days before screening
- Any disorder, except for conditions associated with diabetes mellitus, which in the investigator's opinion might jeopardize participant's safety or compliance with the protocol
- Anticipated initiation or change in concomitant medications known to affect weight or glucose metabolism during the trial
- Impaired liver function, defined as alanine aminotransferase ≥ 2.5 times or bilirubin > 1.5 times the upper normal limit at screening
- Renal impairment (estimated glomerular filtration rate < 60 mL/min/1.73 m²)
- Any episodes of diabetic ketoacidosis within the past 90 days prior to the day of screening
- Known hypoglycemic unawareness as indicated by the investigator according to Clarke's questionnaire question 8^a.
- Recurrent severe hypoglycemic episodes within the last year as judged by the investigator
- Any of the following: myocardial infarction, stroke, hospitalization for unstable angina pectoris or transient ischemic attack within the past 180 days prior to the day of screening
- Participants presently classified as being in New York Heart Association (NYHA) Class IV

- Planned coronary, carotid or peripheral artery revascularization known on the day of screening
- Inadequately treated blood pressure defined as Grade 3 hypertension or higher (systolic ≥ 180 mmHg or diastolic ≥ 110 mmHg) at screening.
- Unwilling or unable to avoid acetaminophen throughout the trial

^aInformation on hypoglycemia unawareness will be recorded according to Clarke's questionnaire, question 8 [1].

The investigator must ask the subject in the following way: "To what extent can you tell by your symptoms that your blood glucose is low? Never, Rarely, Sometimes, Often or Always". Participants answering 'never, rarely or sometimes' are considered to have impaired awareness of hypoglycemia.

Training for use of the iLet[®] bionic pancreas (iLet)

Training on the use of the iLet was provided to all participants and caregivers. In particular, these skill sets included:

- Replacement of batteries
- Installing the PumpCart[®] insulin cartridge
- Priming the fluid path
- Priming and inserting the contact detach infusion set
- Replacement and calibration of the Dexcom G5[®] sensor
- Entering a self-monitored blood glucose value into the bionic pancreas
- Use of the meal-announcement feature
- General use of the graphical user interface

- Troubleshooting the iLet for issues such as occlusions, sensor dropouts, alarms and alerts

Non-investigational devices used

- Dexcom G5 for continuous glucose monitoring (CGM)
 - In-use period of 7 days. Regular calibration of CGM was important to ensure accuracy of sensor glucose data. CGM was calibrated twice daily
- Study phone with CGM app (to display CGM values and record self-measured blood glucose [SMBG] values for sensor calibration)
- Remote monitoring app (iLet-RM)
- Blood glucose (BG) meter (Contour® Next One)
- Infusion set with 60 cm tube
- Blood ketone meter (Precision Xtra®)

At visit 2 (randomization), the investigator ensured that participants knew how to use the devices, and appropriate training was provided using relevant manuals.

Table S1. List of investigators, independent ethics committees/institutional review boards

Site no.	Investigator name and address	Name of independent ethics committee/institutional review board	Reference no.
100	Dr S. Russell Massachusetts General Hospital Diabetes Research Center, Boston, MA, USA	Partners Human Research Committee, Partners Health Care, Somerville, MA, USA	IRB00010760

Table S2. Participant baseline characteristics

	Cohort 1 (t₅₀)	Cohort 2 (t₄₀)	Cohort 3 (t₃₀)
Age, years	45.5 (13.5)	36.3 (14.8)	47.1 (10.7)
Gender, <i>n</i> (%)			
Female	6 (75.0)	7 (87.5)	5 (62.5)
Male	2 (25.0)	1 (12.5)	3 (37.5)
BMI, kg/m ²	28.3 (4.4)	24.1 (3.5)	28.8 (3.9)
Duration of diabetes, years	32.97 (13.69)	16.57 (14.72)	33.13 (10.05)
A1C, %	7.41 (0.52)	7.08 (0.38)	7.85 (0.84)
A1C, mmol/mol	57.52 (5.71)	53.83 (4.12)	62.30 (9.18)
Bolus insulin, <i>n</i> (%)			
IAsp	2 (25.0)	1 (12.5)	0 (0.0)
ILis	6 (75.0)	7 (87.5)	8 (100.0)

Data are mean (SD) unless otherwise stated.

BMI, body mass index; A1C, glycated hemoglobin; IAsp, insulin aspart; ILis, insulin lispro; *n*, number of participants; SD, standard deviation; t₃₀ = 30 min; t₄₀ = 40 min; t₅₀ = 50 min.

Table S3. Number of meal announcements according to relative size of the meal (full analysis set)

	t₅₀ faster aspart			t₆₅ faster aspart			t₄₀ faster aspart			t₆₅ faster aspart			t₃₀ faster aspart			t₆₅ faster aspart		
	Cohort 1			Cohort 1			Cohort 2			Cohort 2			Cohort 3			Cohort 3		
	<i>n</i> (%)	E	R	<i>n</i> (%)	E	R	<i>n</i> (%)	E	R	<i>n</i> (%)	E	R	<i>n</i> (%)	E	R	<i>n</i> (%)	E	R
All	8 (100.0)	152	2.8	8 (100.0)	151	2.7	8 (100.0)	149	2.7	8 (100.0)	130	2.5	8 (100.0)	170	3.2	7 (100.0)	144	3.0
“Tiny”	3 (37.5)	8	0.1	4 (50.0)	9	0.2	3 (37.5)	15	0.3	3 (37.5)	5	0.1	3 (37.5)	4	0.1	3 (42.9)	6	0.1
“Small”	6 (75.0)	21	0.4	6 (75.0)	29	0.5	5 (62.5)	20	0.4	5 (62.5)	10	0.2	7 (87.5)	38	0.7	6 (85.7)	28	0.6
“Typical for me”	8 (100.0)	108	2.0	8 (100.0)	85	1.5	8 (100.0)	89	1.6	8 (100.0)	97	1.8	8 (100.0)	103	1.9	7 (100.0)	98	2.0
“Large”	6 (75.0)	15	0.3	7 (87.5)	28	0.5	5 (62.5)	25	0.4	7 (87.5)	18	0.3	6 (75.0)	25	0.5	6 (85.7)	12	0.2

Meal announcements were entered by the participants via a user interface included in the iLet. Participants were recommended to use this

feature immediately before eating the main meals of the day, but not snacks.

t₃₀ = 30 min; t₄₀ = 40 min; t₅₀ = 50 min; t₆₅ = 65 min; faster aspart, fast-acting insulin aspart; *n*, number of participants with meal announcements; E, number of meal announcements; R, number of meal announcements per day.

Table S4. Time spent in low sensor glucose (<54 mg/dL [3.0 mmol/L]; supplementary statistical analysis – full analysis set)

	t₅₀ faster aspart	t₆₅ faster aspart	t₄₀ faster aspart	t₆₅ faster aspart	t₃₀ faster aspart	t₆₅ faster aspart
	Cohort 1	Cohort 1	Cohort 2	Cohort 2	Cohort 3	Cohort 3
<i>n</i>	8	8	8	8	8	7
LS mean ^a , %	0.98	0.89	0.69	0.50	0.61	0.44
Treatment difference versus t ₆₅ faster aspart (95% CI)	-	0.09 (-0.43;0.61)	-	0.18 (-0.41;0.78)	-	0.17 (-0.17;0.52)
<i>p</i> -value ^b		0.693		0.479		0.247

^aTime spent in low sensor glucose was calculated as the percentage of available sensor glucose values below the threshold, <54 mg/dL (3.0 mmol/L). In this supplementary analysis of the primary endpoint, the default time to maximal serum drug concentration (t_{max}) setting was compared with each of the non-default t_{max} settings separately by cohort for time spent in low sensor glucose, using a linear mixed effect model with treatment and period as fixed effects and participant as random effect.

^b*p*-values are from the 2-sided test for treatment difference evaluated at the 5% level of significance.

CI, confidence interval; faster aspart, fast-acting insulin aspart; LS, least squares; n , number of participants; SD, standard deviation; t_{30} , 30 min; t_{40} , 40 min; t_{50} , 50 min; t_{65} , 65 min; $t_{\max}$, time to maximal serum drug concentration.

Table S5. Time spent in low sensor glucose using different blood glucose thresholds (derivations – descriptive statistics – full analysis set)

	t₅₀ faster aspart	t₆₅ faster aspart	t₄₀ faster aspart	t₆₅ faster aspart	t₃₀ faster aspart	t₆₅ faster aspart
	Cohort 1	Cohort 1	Cohort 2	Cohort 2	Cohort 3	Cohort 3
Time in low sensor glucose (<60 mg/dL [3.3 mmol/L])						
<i>n</i>	8	8	8	8	8	7
Mean (SD), %	1.69 (1.02)	1.71 (1.48)	1.13 (0.70)	0.77 (0.99)	1.12 (0.90)	0.68 (0.85)
Time in low sensor glucose (<70 mg/dL [3.9 mmol/L])						
<i>n</i>	8	8	8	8	8	7
Mean (SD), %	3.86 (1.53)	3.88 (2.20)	2.85 (0.96)	2.43 (1.76)	2.93 (1.79)	1.83 (1.79)

Time spent in low interstitial glucose is calculated as the percentage of available interstitial glucose values below the threshold.

Faster aspart, fast-acting insulin aspart; *n*, number of participants; SD, standard deviation; t₃₀, 30 min; t₄₀, 40 min; t₅₀, 50 min; t₆₅, 65 min.

Table S6. Summary of treatment-emergent adverse events

[illegible]

Unlikely ^c	2 (25.0)	2	1323	1 (12.5)	2	1318	1 (12.5)	2	1314	0	0	0	0	0	0	0	0	0
Related to the iLet bionic pancreas																		
Probable ^a	1 (12.5)	1	661	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Possible ^b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Unlikely ^c	1 (12.5)	1	661	1 (12.5)	2	1318	1 (12.5)	2	1314	0	0	0	0	0	0	1 (14.3)	1	757
Related to a technical complaint																		
Yes	1 (12.5)	1	661	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
No	1 (12.5)	1	661	1 (12.5)	2	1318	1 (12.5)	2	1314	0	0	0	0	0	0	1 (14.3)	1	757
Outcome																		
Recovered/ resolved	1 (12.5)	1	661	1 (12.5)	2	1318	1 (12.5)	2	1314	0	0	0	0	0	0	1 (14.3)	1	757

Recovering/ resolving	1 (12.5)	1	661	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Recovered/ resolved with sequelae	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Not recovered/ not resolved	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Fatal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Unknown	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Relationship is based on investigator's assessment.

^a'Probable' was defined as a good reason and sufficient documentation to assume a causal relationship. ^b'Possible' was defined as a causal relationship that was conceivable and could not be dismissed. ^c'Unlikely' was defined as the event being most likely related to etiology other than the trial product.

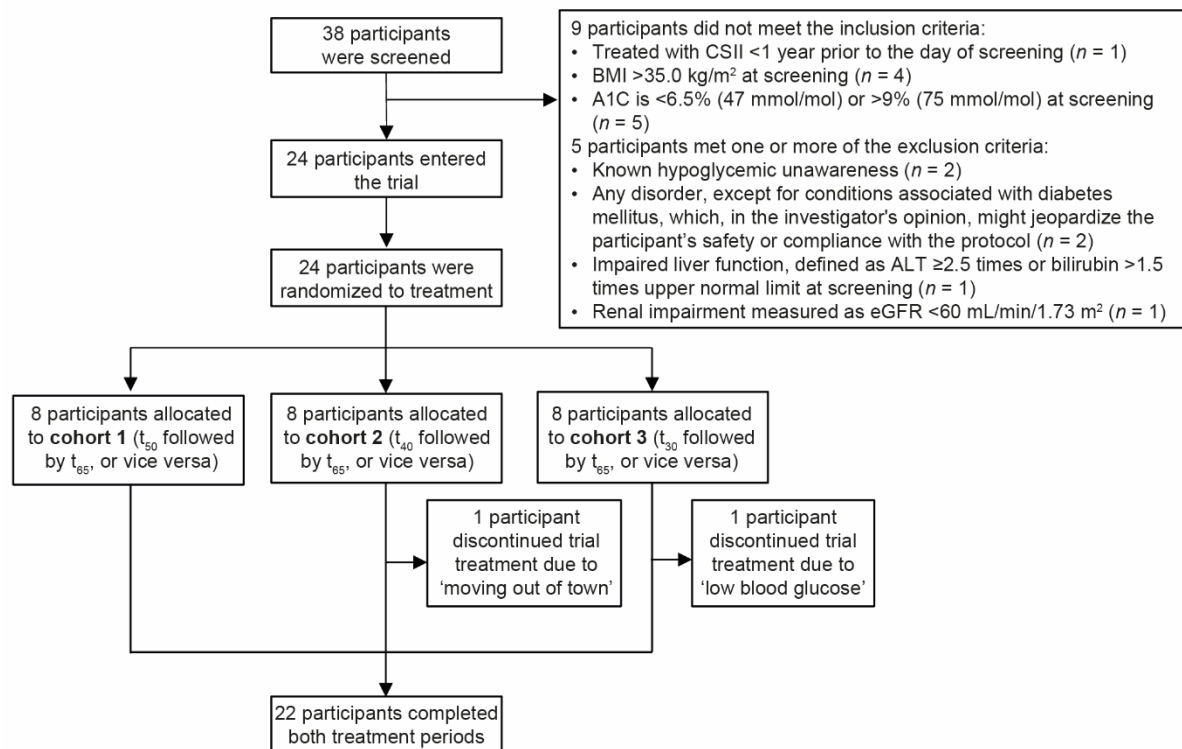
E, number of events; faster aspart, fast-acting insulin aspart; *n*, number of participants; R, event rate per 100 years of exposure; *t*₃₀, 30 min; *t*₄₀, 40 min; *t*₅₀, 50 min; *t*₆₅, 65 min.

Table S7. Infusion-set and PumpCart® changes (safety analysis set)

	t₅₀ faster aspart			t₆₅ faster aspart			t₄₀ faster aspart			t₆₅ faster aspart			t₃₀ faster aspart			t₆₅ faster aspart		
	Cohort 1			Cohort 1			Cohort 2			Cohort 2			Cohort 3			Cohort 3		
	<i>n</i> (%)	E	R	<i>n</i> (%)	E	R	<i>n</i> (%)	E	R	<i>n</i> (%)	E	R	<i>n</i> (%)	E	R	<i>n</i> (%)	E	R
Routine change	7 (87.5)	22	145.5 0	8 (100)	28	184.4 6	8 (100)	22	144.5 9	8 (100)	23	159.12	8 (100)	19	130.6 7	7 (100)	22	166.6 0
Non- routine change	4 (50.0)	5	33.07	3 (37.5)	9	59.29	2 (25.0)	6	39.43	5 (62.5)	7	48.43	5 (62.5)	6	41.26	1 (14.3)	2	15.15
Missing reason	1 (12.5)	1	6.61	1 (12.5)	1	6.59	1 (12.5)	1	6.57	1 (12.5)	1	6.92	3 (37.5)	4	27.51	0	0	0

E, number of events; faster aspart, fast-acting insulin aspart; *n*, number of participants; R, event rate per years of exposure; t₃₀, 30 min; t₄₀, 40 min; t₅₀, 50 min; t₆₅, 65 min.

Figure S1. CONSORT patient flow diagram



ALT, alanine aminotransferase; BMI, body mass index; CSII, continuous subcutaneous insulin infusion; eGFR, estimated glomerular filtration rate; A1C, glycated hemoglobin; n , number of participants; t_{30} , 30 min; t_{40} , 40 min; t_{65} , 65 min.

REFERENCE

1. Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, Polonsky W. Reduced awareness of hypoglycemia in adults with IDDM. A prospective study of hypoglycemic frequency and associated symptoms. *Diabetes Care*. 1995;18:517-22.