Performance of the Insulin-Only iLet Bionic Pancreas and the Bihormonal iLet Using Dasiglucagon in Adults With Type 1 Diabetes in a Home-Use Setting

Luz E. Castellanos,[1] Courtney A. Balliro,[1] Jordan S. Sherwood,[1] Rabab Jafri,[1] Mallory A. Hillard,[1] Evelyn Greaux,[1] Rajendranath Selagamsetty,[2] Hui Zheng,[3] Firas H. El-Khatib,[2] Edward R. Damiano,[2,4] and Steven J. Russell[1]

Diabetes Care 2021;44:e118–e120 | https://doi.org/10.2337/dc20-1086

Reductions in blood glucose levels in people with diabetes are often achieved at the expense of increased hypoglycemia. A novel approach is to automatically deliver microdose glucagon when automation of insulin delivery alone is not sufficient to prevent hypoglycemia. The approach requires a bihormonal device and a stable form of glucagon or glucagon analog. The iLet bionic pancreas (Beta Bionics, Inc.) is a purpose-built, fully integrated device that receives a signal from a continuous glucose monitor (CGM) and contains autonomous, lifelong learning, mathematical dosing algorithms, which are initialized only with the patient's body weight (1). We evaluated the function and safety of the iLet in both its insulin-only configuration and its bihormonal configuration delivering dasiglucagon, a chemically stable glucagon analog (Zealand Pharma), in a home-use study in adults with type 1 diabetes (T1D).

This open-label, random-order, crossover, home-use trial (clinical trial reg. no. NCT03840278, ClinicalTrials.gov) was the first human study to test the bihormonal iLet configuration and the first multiday use of dasiglucagon in people with T1D (2). Ten participants used the insulin-only iLet for 7 days with insulin lispro (Eli Lilly) or aspart (Novo Nordisk), the bihormonal iLet for 7 days with dasiglucagon (4 mg/mL) and insulin lispro or aspart, or both, using the same glucose target (110 mg/dL), in random order. There were no restrictions on diet or exercise. The primary outcomes were prespecified iLet operational thresholds. The key secondary outcome was the median time with CGM glucose <54 mg/dL on days 2–7 (after one day of adaptation).

All participants completed the study. Participants were 21–74 years old and had initial HbA_{1c} levels of 5.7–10.6%. The iLet achieved a CGM capture rate of ≥80% during the insulin-only (90.7%) and bihormonal (88.7%) periods (Table 1). Drug dosing was available >95% of the time (99.7% and 99.1% for insulin in the insulin-only and bihormonal periods, respectively, and 99.7% for dasiglucagon). The ratio of delivered to attempted drug volume was 95–105% (100.3% and 99.9% for insulin in the insulin-only and bihormonal periods, respectively, and 102.0% for dasiglucagon).

The median percentage of time with CGM glucose <54 mg/dL was 0.6% (interquartile range [IQR] 0.2–1.1%) and 0.2% (IQR 0–0.4%) in the insulin-only and bihormonal periods, respectively (Table 1). The mean CGM glucose and time in range (70–180 mg/dL) were 149 ± 13 mg/dL and 72 ± 8%, respectively, in the insulin-only period, and 139 ± 11 mg/dL and 79 ± 9%, respectively, in the bihormonal period. The mean daily carbohydrates consumed to prevent or treat hypoglycemia were 16 ± 13 g and 18 ± 21 g in the insulin-only and bihormonal periods, respectively.

The mean total daily dose (TDD) of dasiglucagon was 0.35 mg/day. All subjects used one prefilled dasiglucagon cartridge for the entire 7-day period. The average daily nausea scores on a 0–10 visual analog scale were 0.07 ± 0.12 cm and 0.47 ± 0.83 cm in the insulin-only and bihormonal periods, respectively. One participant reported an episode of vomiting during the bihormonal period.

There were five instances of confirmed insulin leakage at the insulin cartridge connector (one in the bihormonal and four in the insulin-only period) that led to replacement of the insulin cartridge and connector. In participants who had confirmed leaks, the insulin TDD was 1.4–3.3-fold higher (mean TDD 1.3 vs. 0.6 units/kg/day) and the mean CGM glucose was 30–72 mg/dL higher (mean 197 vs. 139 mg/dL) on days with

[1]*Massachusetts General Hospital Diabetes Research Center, Boston, MA*
[2]*Beta Bionics, Inc., Concord, MA*
[3]*Massachusetts General Hospital Biostatistics Center, Boston, MA*
[4]*Department of Biomedical Engineering, Boston University, Boston, MA*
Corresponding author: Steven J. Russell, sjrussell@mgh.harvard.edu

Received 8 May 2020; and accepted 1 March 2021

Clinical trial reg. no. NCT03840278, clinicaltrials.gov

Table 1—Summary of results

	iLet operational performance targets	Insulin-only iLet	Bihormonal iLet
iLet operational outcomes			
CGM glucose readings captured, %	≥80	90.7	88.7
Insulin delivery channel availability, %	≥95	99.7	99.1
Ratio of cumulative delivered to attempted insulin volume, %	95–105	100.3	99.9
Glucagon delivery channel availability, %	≥95		99.7
Ratio of cumulative delivered to attempted glucagon volume, %	95–105		102.0
CGM glucose outcomes	ADA consensus targets (3)	Insulin-only iLet	Bihormonal iLet
Median % of time <54 mg/dL (IQR)	<1	0.6 (0.2–1.1)	0.2 (0–0.4)
Median % of time <70 mg/dL (IQR)	<4	4.0 (2.8–4.8)	2.0 (1.3–3.3)
Mean CGM glucose, mg/dL (SD)		149 (13)	139 (11)
Mean % of time 70–180 mg/dL (SD)	>70	72 (8)	79 (9)
Mean % of time >180 mg/dL (SD)	<25	24 (8)	18 (8)
Mean % of time >250 mg/dL (SD)	<5	6 (5)	4 (4)
Mean coefficient of variation, % (SD)	<36	38 (7)	36 (7)
Mean standard deviation, mg/dL (SD)		57 (14)	50 (13)
Nonglycemic outcomes			
Mean daily carbohydrates for prevention or treatment of hypoglycemia, g (SD)		16 (13)	18 (21)
Dasiglucagon doses, mg/day (SD)			0.35 (0.13)
Insulin doses, unit/kg/day (SD)		0.72 (0.23)	0.60 (0.19)

As prespecified, iLet operational outcomes are reported for days 1–7, and CGM glucose outcomes and nonglycemic outcomes are reported for days 2–7. ADA, American Diabetes Association.

confirmed leaks than on days in the same arm without documented leaks.

There were no occlusions or infusion site reactions. There was no severe hypoglycemia or diabetic ketoacidosis, and there were no serious or unexpected adverse events.

Both iLet configurations met the prespecified operational performance targets. However, leaks occurred at the insulin cartridge connector. This was due to off-center piercing of the cartridge septum prior to insertion into the iLet that led to leakage through an enlarged hole in the septum after needle insertion. This observation led to changes in the cartridge replacement procedure and to design changes in the next-generation cartridge connector and iLet that will be used in the pivotal clinical trial. Despite insulin leakage, the mean CGM glucose and time in range were similar to those observed in previous trials, likely due to autonomous adaptation of insulin dosing by the iLet algorithms.

The mean TDD of dasiglucagon was comparable to that of freshly reconstituted human glucagon observed in previous bionic pancreas trials (1). Time with glucose <54 mg/dL was <1% in both arms, consistent with the American Diabetes Association target for this metric (3). The use of a single, prefilled dasiglucagon cartridge for 7 days with no infusion site reactions or occlusions supports the practicality for this liquid formulation in clinical use. These results support testing the next-generation iLet with dasiglucagon in much larger and longer pivotal trials.

Acknowledgments. The authors thank the participants for their time and effort; the diabetes care providers who referred potential participants to the study staff; the Massachusetts General Hospital (MGH) Diabetes Research Center study staff, Mary Larkin, Camille Staco-Targete, Nancy Kingori, Stephanie Dimodica, Khadija Tlaiti, and the Diabetes Research Center, MGH, for organizational and logistical support; Michele Sullivan for participating in the conduct of the trial; Camille Powe, Kerry Grennan, and Takara Stanley (MGH Pediatric Endocrine Division) for serving on the data safety and monitoring board for the study; and the members of the Partners Human Research Committee.

Funding. L.E.C. received funding from National Institute of Diabetes and Digestive and Kidney Diseases grant 3R01-DK-119699-01S1. J.S.S. received funding from National Institute of Diabetes and Digestive and Kidney Diseases grant T32-DK-007028. Zealand Pharma donated the dasiglucagon for the study. This study was funded by Beta Bionics (Study 19-002).

Duality of Interest. C.A.B. has received consulting fees from Beta Bionics and Novo Nordisk. E.R.D., F.H.E.-K., and R.S. are inventors on patents and patents pending related to the bionic pancreas technology. E.R.D. and F.H.E.-K. are employees, cofounders, and equity holders in Beta Bionics, Inc. E.R.D. is on the Board of Directors of Beta Bionics, Inc. R.S. is an employee in, and holds options to purchase stock in, Beta Bionics, Inc. S.J.R. is an inventor on a patent and patents pending on aspects of the bionic pancreas that are assigned to Massachusetts General Hospital and are licensed to Beta Bionics; has received honoraria and/or travel expenses for lectures from Novo Nordisk, Roche, and Ascensia; serves on the scientific advisory boards of Unomedical and Companion Medical; has received consulting fees from Beta Bionics, Novo Nordisk, Senseonics, and Flexion Therapeutics; has received grant support from Zealand Pharma, Novo Nordisk, and Beta Bionics; and has received in-kind support in the form of technical support and/or donation of materials from Zealand Pharma, Ascencia, Senseonics, Adocia, and Tandem Diabetes. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. L.E.C. and E.G. wrote the first draft of the letter. L.E.C., H.Z., and S.J.R. interpreted the data. C.A.B., J.S.S., R.J., M.A.H., E.G., R.S., F.H.E.-K., E.R.D., and S.J.R. participated in revision of the letter for important intellectual content. C.A.B., R.J., M.A.H., E.G., and S.J.R. enrolled and screened participants for the study and conducted study visits. C.A.B., F.H.E.-K., E.R.D., and S.J.R. designed the study. H.Z. performed the data analysis. F.H.E.-K. and E.R.D. designed the iLet. S.J.R. supervised the human studies. S.J.R. 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.

References

1. El-Khatib FH, Balliro C, Hillard MA, et al. Home use of a bihormonal bionic pancreas versus insulin pump therapy in adults with type 1 diabetes: a multicentre randomised crossover trial. Lancet 2017;389:369–380

2. Hövelmann U, Bysted BV, Mouritzen U, et al. Pharmacokinetic and pharmacodynamic chara cteristics of dasiglucagon, a novel soluble and stable glucagon analog. Diabetes Care 2018;41: 531–537

3. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: re-commen dations from the international consensus on time in range. Diabetes Care 2019;42:1593–1603