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

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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 HbA1c 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

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

There were no oclusions 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 in much larger and longer pivotal trials.

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#### Duality of Interest

C.A.B., F.H.E.-K., E.R.D., and S.J.R. designed the study. 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.

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