



Clinical Impact of ITCA 650, a Novel Drug-Device GLP-1 Receptor Agonist, in Uncontrolled Type 2 Diabetes and Very High Baseline HbA_{1c}: The FREEDOM-1 HBL (High Baseline) Study

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OBJECTIVE

ITCA 650 is a subdermal osmotic mini-pump that continuously delivers exenatide subcutaneously for 3–6 months. The efficacy, safety, and tolerability of ITCA 650 added to diet and exercise alone or combined with metformin, sulfonylurea, or thiazolidinedione monotherapy or a combination of these drugs was evaluated in poorly controlled patients with type 2 diabetes (T2D) who were ineligible for participation in a placebo-controlled study (FREEDOM-1) because of severe hyperglycemia (HbA_{1c} >10% [86 mmol/mol]).

RESEARCH DESIGN AND METHODS

This 39-week, open-label, phase 3 trial enrolled patients aged 18–80 years with HbA_{1c} >10% to ≤12% (86–108 mmol/mol) and BMI 25–45 kg/m². Patients received ITCA 650 20 μg/day for 13 weeks, then 60 μg/day for 26 weeks. The primary end point was change in HbA_{1c} at week 39.

RESULTS

Sixty patients were enrolled. At baseline, mean HbA_{1c} was 10.8% (94.7 mmol/mol) and mean (± SD) duration of diabetes was 8.6 (± 5.3) years. At week 39, there was a mean reduction in HbA_{1c} of –2.8% (–30.3 mmol/mol; *P* < 0.001 vs. baseline) and in body weight of –1.2 kg (*P* = 0.105), and 25% of patients achieved HbA_{1c} <7% (53 mmol/mol). A reduction in HbA_{1c} of ≥1% (≥10.9 mmol/mol) occurred in 90% of patients. The most common adverse events were nausea, vomiting, diarrhea, and headache. Gastrointestinal adverse events were generally transient and subsided over time; only 4 patients (6.7%) discontinued for gastrointestinal events.

CONCLUSIONS

Treatment with ITCA 650, the first injection-free glucagon-like peptide 1 receptor agonist, resulted in significant improvements in glycemic control in poorly controlled long-standing T2D patients with a high baseline HbA_{1c} >10%.

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Over 50% of patients with type 2 diabetes (T2D) have inadequate glycemic control (1,2) despite the availability of an increasing number of effective therapies (3,4). Severely hyperglycemic patients may contribute disproportionately to the burden of diabetes (5), and most guidelines recommend initiation of insulin therapy. In the National Health and Nutrition Examination Survey (NHANES), 12.6% of patients with T2D had HbA_{1c} >9% (75 mmol/mol) (1). A Canadian registry of diabetes specialty clinics reported that 16.1% of patients with T2D had an HbA_{1c} level of at least 9% (75 mmol/mol) (5). Between 38% and 54% of patients have appropriate adherence to antidiabetes drugs as defined by percent of patients with ≥80% of days covered (6). Medication nonadherence limits the realization of the full efficacy of therapy, results in poor health outcomes, and has a negative impact on society as a result of increased health care resource utilization and cost (4,7,8). Nonadherence to therapy, especially insulin or injectable glucagon-like peptide 1 receptor agonists (GLP-1 RAs), may be the most significant contributing factor to poor glycemic control in a high-risk group with severe hyperglycemia (9).

GLP-1 RAs have emerged as important therapeutic agents for the treatment of T2D, lowering glucose and promoting weight loss while posing a low risk of hypoglycemia (10) because of their glucose-dependent effect on insulin secretion (11). Although the GLP-1 agonists produce significant improvements in glycemic control, the disadvantage of all currently approved GLP-1 agonists is the need for daily or weekly injections, resulting in low adherence to and persistence of therapy. Indeed, approximately 35% of patients were adherent to injectable GLP-1 agonist therapy during a 12-month period (12), and persistence rates of 30–36% were reported over a 12-month follow-up (6,13).

Effective T2D therapies must be efficacious and safe while also addressing the issue of medication nonadherence. More innovative approaches for drug delivery are needed in order to improve long-term glycemic control and patient outcomes.

ITCA 650 provides an innovative method of delivering exenatide, which has the potential to address important and prevalent unmet medical needs of patients with T2D by improving and sustaining glycemic control over time. ITCA

650 is a drug-device combination product in development for the treatment of T2D (Supplementary Fig. 1). It consists of a small titanium matchstick-sized osmotic mini-pump that delivers a continuous subcutaneous infusion of exenatide for extended periods (14,15). Placement and removal of ITCA 650 are performed by trained health care professionals using local anesthesia during a brief office procedure that has been well tolerated by patients. The sterile mini-pump is placed in the subdermis of the abdominal wall using a placement tool and is removed or replaced through a small (~5 mm) incision that is closed with Steri-Strips. ITCA 650 can be easily removed in a physician's office to rapidly terminate drug administration if necessary, as exenatide levels fall rapidly within 24 h after removal (16).

In a randomized, 24-week, open-label, phase 2 study, patients with T2D inadequately controlled with metformin who were treated with ITCA 650 20 μg/day for 12 weeks followed by 60 μg/day for 12 weeks experienced significant reductions in HbA_{1c} of -1.4% (-8.2 mmol/mol) and in body weight of -3.1 kg after the 24-week treatment period (17); these effects were maintained during a 24-week extension (18). In a randomized, double-blind, placebo-controlled phase 3 study, ITCA 650 demonstrated significant reductions in HbA_{1c} and body weight compared with placebo and was well tolerated (19). We report here the results from the open-label cohort of patients from this study who were not eligible to participate in the placebo-controlled trial because of baseline HbA_{1c} >10% (86 mmol/mol).

RESEARCH DESIGN AND METHODS

The study was approved by an institutional review board and conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation Guideline for Good Clinical Practice. All patients gave written informed consent. A Data Monitoring Committee was responsible for evaluating cumulative safety data at regular intervals. Independent cardiovascular end point adjudication and clinical events committees reviewed and adjudicated suspected major adverse cardiovascular events, thyroid cancer, pancreatic cancer, and pancreatic events in a blinded manner.

Investigative site personnel were provided with kits containing all supplies

necessary to conduct the procedures and were trained and certified via a standardized online and hands-on training program prior to the initiation of any study procedures.

Study Design

This open-label phase 3 study was conducted at 32 clinical sites in the U.S. and consisted of a 4-week screening period, a 39-week treatment period, and a 4-week posttreatment follow-up period (Supplementary Fig. 2). Enrolled patients had been screened for participation in the FREEDOM-1 trial, a 39-week randomized, double-blind, placebo-controlled trial with ITCA 650 (19) but were excluded because they did not meet glycemic inclusion criteria of HbA_{1c} ≤10% (86 mmol/mol).

Patients were initially treated with ITCA 650 20 μg/day for 13 weeks. The device was placed subdermally in the abdominal wall using local anesthesia. At the 13-week visit, the 20 μg/day mini-pump was removed and replaced, usually at the same site, with a 60 μg/day mini-pump for the subsequent 26 weeks.

Patient Selection

Eligible patients were males and females with T2D, age 18 to 80 years, with HbA_{1c} >10% (86 mmol/mol) and ≤12% (108 mmol/mol), fasting plasma glucose (FPG) ≤300 mg/dL, BMI ≥25 to ≤45 kg/m², and serum calcitonin <50 ng/L who were receiving stable (≥3 months prior to screening) treatment with diet and exercise alone or with metformin (≥1,500 mg/day), sulfonylureas (SUs) (≥ half maximal dose), or pioglitazone (≥30 mg/day) monotherapy or in combination.

Patients were excluded if they previously had received a GLP-1 RA; took dipeptidyl peptidase 4 (DPP-4) inhibitors, α-glucosidase inhibitors, meglitinides, sodium-glucose cotransporter 2 (SGLT2) inhibitors, or insulin (except short-term treatment) within 3 months of screening; or had an estimated glomerular filtration rate <60 mL/min/1.73 m².

Patients were required to maintain their baseline dose of background medication throughout the study. Investigators could titrate the dose of SUs downward to avoid and/or treat hypoglycemia and were expected to assess contributing factors for hypoglycemia.

Patients with unacceptable hyperglycemia were expected to receive additional

antidiabetes treatment and continue in the study. Criteria for rescue therapy became more stringent as the study progressed beyond week 13 such that by week 26 additional antidiabetes treatment was required if HbA_{1c} was >8.5% (63.9 mmol/mol) (see Supplementary Data). Insulin glargine titrated to target FPG was recommended; additional oral antidiabetes medication could be added instead, at the discretion of the investigator, but DPP-4 inhibitors, other GLP-1 RAs, and SGLT2 inhibitors were not allowed for rescue therapy.

Study Assessments

Blood samples were collected at prespecified time points and analyzed at the central laboratory (Quintiles Laboratories Ltd., Marietta, GA) to determine levels of HbA_{1c}, FPG, fasting lipids (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, apolipoprotein B-100), adiponectin, insulin, and high-sensitivity C-reactive protein. Safety assessments included adverse events (AEs), clinical laboratory measurements (chemistry including amylase, lipase, calcitonin, and thyroid-stimulating hormone, hematology, and urinalysis), 12-lead electrocardiogram, vital signs, and physical examinations. Antiexenatide antibodies (ADAs) were determined in human serum samples using a validated ELISA (Charles River Laboratories [formerly WIL Research], Skokie, IL).

The primary end point was the change from baseline in HbA_{1c} at week 39. Key secondary end points were change in body weight and percentage of patients achieving HbA_{1c} <7% (<53 mmol/mol).

AEs of special interest included major adverse cardiovascular events, gastrointestinal AEs (nausea/vomiting), pancreatitis, pancreatic cancer, thyroid cancer, hypoglycemia, and procedural/application site AEs. Hypoglycemia was defined as minor if symptoms were accompanied by plasma glucose <60 mg/dL (3.3 mmol/L). A major hypoglycemic event was defined when hypoglycemic symptoms required the assistance of a third party to actively administer resuscitative measures.

Statistical Methods

The sample size was based on the assumption that a reduction of at least 0.7% (7.1 mmol/mol) in HbA_{1c} would occur after 39 weeks of treatment; a CI with a half-width of 0.7% (7.1 mmol/mol) was desired. Assuming an interpatient standard

deviation of 1.25 and a dropout rate of up to 30% through the end of the 39-week treatment period, 51 patients were needed for a 90% power to achieve the desired precision.

The safety (SAF) population included all patients who had a procedure started for ITCA 650 placement. The modified intent-to-treat (mITT) population included all subjects from the SAF population who had a valid baseline and at least one post-baseline HbA_{1c} value. The efficacy evaluable population included the patients in the mITT population who had baseline and week 39 HbA_{1c} values, did not require rescue therapy, and had no major protocol deviations through week 39. All safety analyses were based on the SAF population, and all efficacy analyses were based on the mITT population. The primary end point was mean change from baseline to week 39 in HbA_{1c}. The last observation carried forward (LOCF) method was used to address missing values for efficacy. Patients that terminated early from study treatment were included with their last postbaseline HbA_{1c} value carried forward. Patients who took rescue therapy were included with their last postbaseline HbA_{1c} value before beginning rescue therapy carried forward.

The analysis included the 95% CI and each time point, and a one-sample *t* test was used to evaluate whether the change from baseline was different from 0. The effect of age, sex, and background treatment (e.g., SU or thiazolidinedione monotherapy) on the change in HbA_{1c} was explored through linear models. Mean change in body weight as a secondary end point was analyzed similarly to the primary end point. Mixed effects models for repeated measures, another method for handling missing data, were conducted for HbA_{1c} and weight as sensitivity analyses. The proportion of patients attaining an HbA_{1c} level of <7% (53 mmol/mol) at week 39 was determined using a logistic regression model with proportion of patients with HbA_{1c} <7% (53 mmol/mol) at LOCF end point as the outcome variable. Other end points, such as changes in blood lipids (total, LDL, and HDL cholesterol, triglycerides, and apolipoprotein B-100), systolic and diastolic blood pressure, and FPG at week 39, were evaluated as well.

Safety was assessed primarily through summaries of AEs, hypoglycemic episodes, clinical laboratory tests, physical examinations, vital signs, electrocardiograms, and the presence of ADAs.

Table 1—Baseline demographic and clinical characteristics, safety population (N = 60)

Characteristic	Value
Age, years	51.9 ± 10.2
Age range, years	25–70
Age ≥65 years	9 (15.0)
Male	34 (56.7)
Race	
White	48 (80.0)
Black or African American	8 (13.3)
Other	4 (6.7)
Hispanic or Latino	23 (38.3)
Body weight, kg	92.9 ± 18.8
BMI, kg/m ²	32.0 ± 4.9
BMI ≥30 kg/m ²	38 (63.3)
HbA _{1c} , % (mmol/mol)	10.8 ± 0.7 (94.7 ± 7.1)
FPG (mmol/L)	13.7 ± 3.0
Estimated GFR (mL/min/BSA)	96.2 ± 21.5
Years since diabetes diagnosis	8.5 ± 5.3
Antidiabetes treatment at baseline	
Diet and exercise	18 (30.0)
Metformin	21 (35.0)
SU	1 (1.7)
Metformin + SU	19 (31.7)
Metformin + SU + TZD	1 (1.7)

Data are mean ± SD or *n* (%) unless otherwise indicated. BSA, body surface area; GFR, glomerular filtration rate; TZD, thiazolidinedione.

RESULTS

Sixty patients were enrolled and treated with ITCA 650, and 59 (98.3%) had at least one postbaseline HbA_{1c} result (mITT population). Fifty-two (86.7%) patients completed treatment for 39 weeks. Of the eight (13.3%) patients who discontinued, one (1.7%) withdrew consent, six (10.0%) withdrew for an AE, and one (1.7%) was lost to follow-up. Twenty (33.3%) patients received rescue therapy and continued in the study. The mean time to rescue was 164.5 ± 61.4 days; over half of patients were rescued after week 26 based on protocol criteria requiring HbA_{1c} to be ≤8.5% (63.9 mmol/mol).

Baseline demographic and clinical characteristics were representative of patients with long-standing poorly controlled T2D (Table 1). The mean baseline HbA_{1c} was 10.8% ± 0.7% (94.7 ± 7.1 mmol/mol). Most patients were obese with diagnosed hypertension and dyslipidemia. The mean duration of diabetes was 8.6 ± 5.3 years. Twenty-one patients (35%) were taking metformin monotherapy and 19 (32%) were on metformin and an SU. Approximately 30% of patients were not taking any antidiabetes medication at baseline, although most had previously received antidiabetes therapy.

Efficacy

Glycemic Control

A clinically meaningful significant decrease in HbA_{1c} from baseline was observed in the mITT population. The mean ± SD change from baseline to week 39 LOCF end point for HbA_{1c} was -2.8 ± 1.4% (95% CI -3.1, -2.4) (-30.3 ± 15.5 mmol/mol [95% CI -34.4, -26.3]; *P* < 0.001 vs. baseline). The repeated measures sensitivity analysis was consistent with the primary analysis, resulting in an adjusted mean change (± SE) in HbA_{1c} of -3.0 ± 0.2% (-9.3 ± 2.6 mmol/mol). The efficacy evaluable population (33 patients) had a mean ± SD change from baseline in HbA_{1c} of -3.4 ± 1.3% (95% CI -3.9, -2.9) (-13.7 ± 9.3 mmol/mol [95% CI -19.1, -8.2]; *P* < 0.001 vs. baseline).

Significant reductions in HbA_{1c} were seen as early as week 6 after starting treatment (Fig. 1A), continued through the dose escalation at week 13, reached a plateau at week 32, and persisted through week 39. In the mITT population, the mean ± SD change from baseline to week 39 LOCF end point for FPG

was -61 ± 72 mg/dL (-3.4 ± 4.0 mmol/L [95% CI -4.5, -2.4]; *P* < 0.001 vs. baseline).

Proportion of Patients With HbA_{1c} <7% and Other HbA_{1c} Analyses

At week 39, 15 patients (25.4% [95% CI 15.0, 38.4]) reached the HbA_{1c} goal of <7% (53 mmol/mol) and 11 patients (18.6% [95% CI 9.7, 30.9]) achieved an HbA_{1c} level of ≤6.5% (48 mmol/mol). The proportions of patients with a reduction in HbA_{1c} of ≥2% (16.4 mmol/mol) and ≥3% (9.3 mmol/mol) were 73% and 46%, respectively (Fig. 1B). Predefined subgroup analyses revealed similar statistically significant (*P* < 0.001 vs. baseline) reductions in HbA_{1c} by background therapy.

Change in Body Weight

The mean ± SD change from baseline to week 39 for body weight in the mITT population was -1.2 ± 5.8 kg (95% CI -2.7, 0.3; *P* = 0.105 vs. baseline), which was not statistically significant.

Other Outcomes

Changes from baseline for total cholesterol, LDL cholesterol, and HDL cholesterol were small and not significant. Mean ± SD levels of triglycerides and apolipoprotein B-100 decreased by 0.37 ± 1.04 mmol/L (*P* = 0.035) and 0.12 ± 0.30 g/L (*P* = 0.023), respectively (Supplementary Table 1). Small, nonsignificant increases from baseline in both mean systolic (0.8 ± 12.4 mmHg) and diastolic (1.5 ± 7.0 mmHg) blood pressure

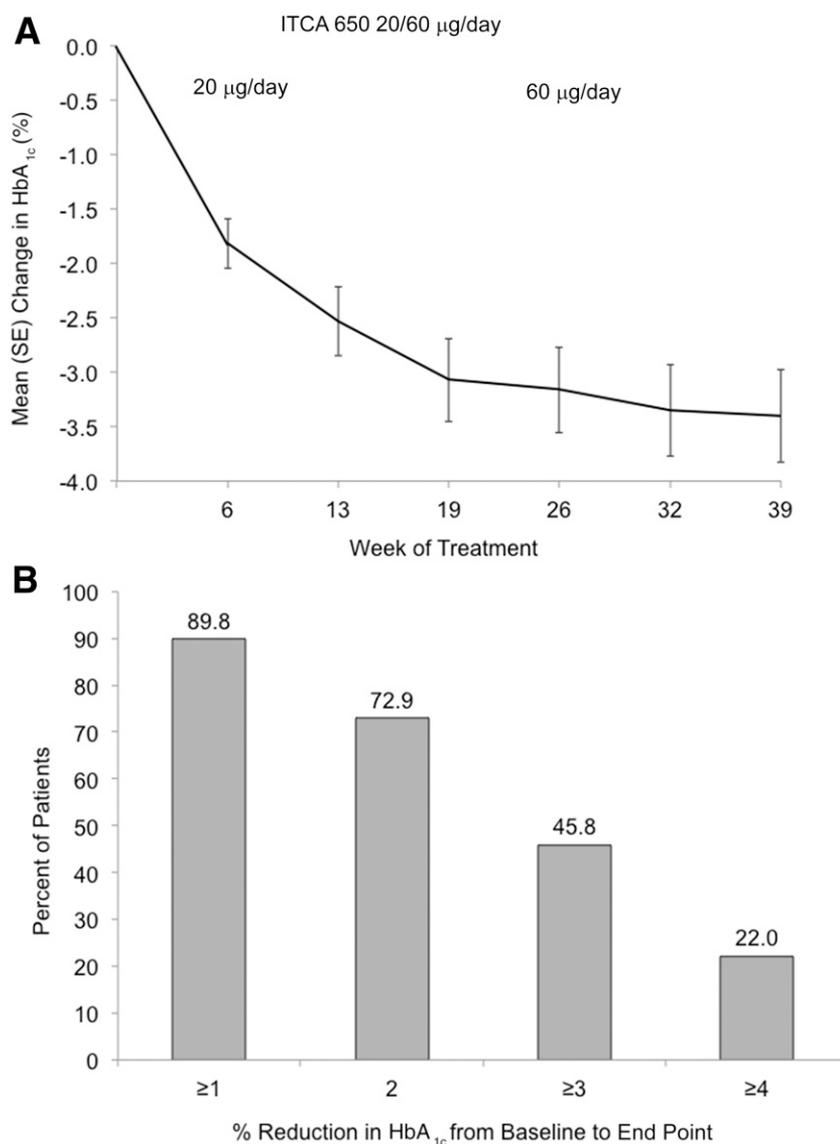


Figure 1—A: Mean (SE) change in HbA_{1c} from day 0 to week 39 (mITT population, excludes data postrescue). B: Proportion of patients achieving HbA_{1c} reductions (mITT population).

and in heart rate (4.5 bpm) were observed (Supplementary Table 2).

Tolerability

The proportion of patients who reported at least one AE was 86.7%. Six serious AEs were reported in four patients, all considered by the investigator to be unrelated to ITCA 650 therapy. A total of eight patients (13.3%) discontinued from the study. Discontinuation due to AEs occurred in six patients (10.0%), four because of gastrointestinal disorders (nausea, vomiting, and diarrhea). The most common treatment-emergent AEs were gastrointestinal disorders (Table 2). The incidence of nausea was highest during the first week after treatment initiation and dose escalation and then diminished thereafter toward baseline (Fig. 2). Minor hypoglycemic events occurred in four (6.7%) patients, three in patients taking SUs as background therapy and one after initiation of rescue medication with insulin. No major hypoglycemic events were reported. There was one death (sudden cardiac death), which was not considered related to study treatment. No thyroid cancer, pancreatic cancer, or pancreatitis was observed.

The most frequently reported AEs related to the administration site were bleeding (15.0%), pain (6.7%), and bruising (5.0%), which were mostly mild, transient, and consistent with expectations from a minor medical procedure. There were 178 study procedures to place, replace, and remove study devices. Three removals were not successful at first attempt (reported as “device removal failed”), primarily due to initial placement of the device being too deep in the subcutaneous tissue. Two of the three removal procedures were successful during a subsequent attempt by the investigator, but one required referral to a specialist (assisted removal) who successfully removed the device. One device was not located at the final removal visit and was confirmed by imaging to not be present. This device was assumed to have been extruded shortly after the placement procedure. One patient experienced cellulitis at the application site, which was treated with topical and oral antibiotics. All events were assessed by investigators as mild in severity and none resulted in discontinuation of the patient from the study.

A small increase from baseline was observed for serum amylase (14.0 ± 17.5

units/L) and serum lipase (16.7 ± 31.8 units/L) at week 39, but these increases were within normal limits and did not correlate with clinical signs or symptoms (Supplementary Table 2). Positive ADAs were detected in 10 (16.7%) patients; the incidence was 16% at week 13 and decreased to 3.4% at week 39. The antibodies in three ADA-positive patients were found to cross-react with GLP-1 at week 13 and were subsequently negative. None of the ADA-positive samples cross-reacted with glucagon. Because of the small number of ADA-positive patients, no conclusion can be made about the impact of ADAs on the primary end point.

CONCLUSIONS

Treatment with ITCA 650 for 39 weeks resulted in a significant and clinically meaningful reduction in HbA_{1c} in poorly controlled patients with T2D receiving antidiabetes therapy or diet and exercise alone. The patient population was obese (65%) with an average duration of diabetes of 8.5 years and baseline HbA_{1c} of 10.8% (94.7 mmol/mol), despite the majority being treated with one or more oral antidiabetes drugs. Background drug therapy was used by 70% of patients, and 20% had discontinued antidiabetes medications within the 12 months before screening. The addition of ITCA 650 resulted in 25% of patients achieving goal HbA_{1c} <7% and 73% of patients having a reduction in HbA_{1c} of ≥2%. One-third of patients received additional “rescue”

Table 2—Incidence of treatment-emergent AEs occurring in >5% of patients or of special interest, safety population (N = 60)

Treatment-emergent AE	n (%)
Nausea	21 (35.0)
Vomiting	16 (26.7)
Diarrhea	14 (23.3)
Application site bleeding	9 (15.0)
Upper respiratory tract infection	7 (11.7)
Headache	5 (8.3)
Hypertension	5 (8.3)
Urinary tract infection	5 (8.3)
Application site pain	4 (6.7)
Constipation	4 (6.7)
Dyspepsia	4 (6.7)
Hypoglycemia, minor*	4 (6.7)

*Minor hypoglycemia was defined as symptoms suggestive of hypoglycemia with a plasma glucose level <60 mg/dL.

therapy, usually after week 26 when protocol-defined rescue criteria required that HbA_{1c} be ≤8.5%. Mean weight loss was modest and not statistically significant. Assessment of goal attainment and reductions in HbA_{1c} and weight were made on data prior to the initiation of rescue therapy.

ITCA 650 was generally well tolerated. Consistent with the GLP-1 RA class, the most common AEs were gastrointestinal (nausea, vomiting, and diarrhea), which decreased over time and were associated with a low incidence of treatment discontinuation. There was a low incidence of minor hypoglycemia, and procedures to

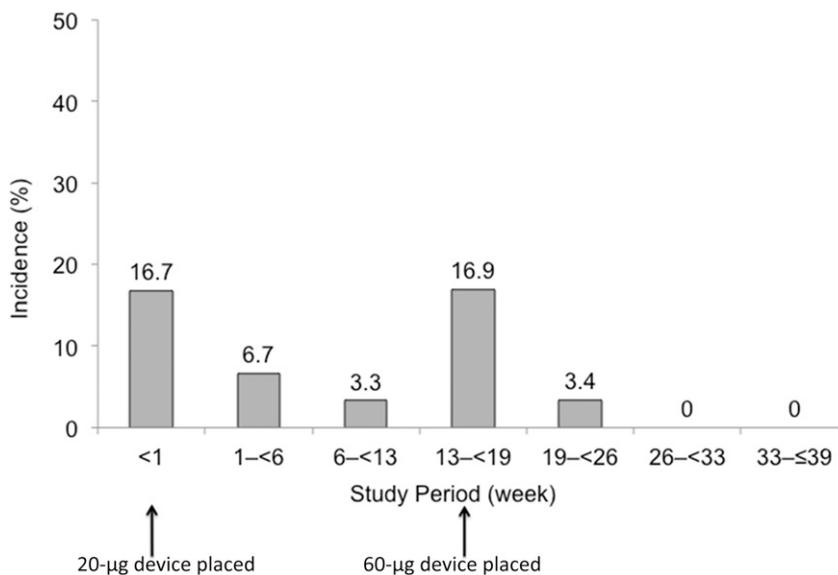


Figure 2—Incidence of nausea over time to week 39.

place and remove the ITCA 650 were well tolerated by patients.

Several open-label studies of patients with T2D and HbA_{1c} levels >10% (86 mmol/mol), treated for 24 weeks with DPP-4 inhibitors or SGLT2 inhibitors combined with metformin (20–25), have reported reductions in HbA_{1c} of similar magnitude to this study. However, in those studies a DPP-4 or SGLT2 inhibitor was started together with metformin, the duration of diabetes was generally shorter, and fewer than 20% of patients reached the American Diabetes Association target of <7%. The modest weight loss observed in this study relative to that reported in the phase 2 and phase 3 studies with ITCA 650 (17,19) and studies with exenatide (26) is likely due to the reversal of caloric losses in the urine as a result of the correction of severe hyperglycemia and is consistent with results of SGLT2 inhibitors in similar high baseline HbA_{1c} populations (20,27).

Patients with HbA_{1c} ≥10% represent 6.8% of the adult U.S. population with diabetes (1). Excessive hyperglycemia is commonly encountered in patients with diabetes in clinical practice and described in retrospective, population-based studies (28,29). In one study with patients taking multiple oral antidiabetes drugs, the baseline HbA_{1c} was >11.8% (96 mmol/mol) in 12.3% of the group starting a GLP-1 agonist and 19.5% of those starting insulin (29). Guidelines generally recommend the initiation of insulin when glycemia reaches this level (30). Treatment of these patients may contribute disproportionately to the burden of diabetes (5).

Once ITCA 650 is placed, no action on the part of the patient is required in order to ensure therapeutic adherence for the 3- or 6-month dosing period. The potential for complete adherence to treatment when the ITCA 650 is in place, combined with the observed treatment effects, may address a key challenge that has profound implications for patients, health care professionals, and payers.

Limitations of this study are the open-label design and relatively small sample size. However, the primary result, although of greater magnitude, is consistent with that of the randomized, double-blind, placebo-controlled trial (FREEDOM-1) (19) for which these patients were originally screened. The patients in the current study met all inclusion/exclusion criteria for FREEDOM-1 except for the level of

hyperglycemia at baseline. As such, the limitations noted are not likely to diminish the conclusion from these data.

In this population of patients with longstanding diabetes and severe hyperglycemia, treatment with ITCA 650 was well tolerated and resulted in a significant and sustained reduction in HbA_{1c}.

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