Efficacy and Safety of ITCA 650, a Novel Drug-Device GLP-1 Receptor Agonist, in Type 2 Diabetes Uncontrolled With Oral Antidiabetes Drugs: The FREEDOM-1 Trial

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OBJECTIVE

ITCA 650 (exenatide in osmotic mini-pump) continuously delivers exenatide subcutaneously for 3–6 months. Two doses of ITCA 650 were compared with placebo in patients with uncontrolled type 2 diabetes.

RESEARCH DESIGN AND METHODS

This 39-week, phase 3, double-blind, placebo-controlled trial randomized 460 patients aged 18–80 years with glycated hemoglobin (HbA_{1c}) 7.5–10% [58–86 mmol/mol] 1:1:1 to placebo, ITCA 650 40 μg/day, or ITCA 650 60 μg/day. Primary end point was change in HbA_{1c} at 39 weeks.

RESULTS

Least squares (LS) mean change from baseline HbA_{1c} was −1.1% [−12.2 mmol/mol] and −1.2% [−13.2 mmol/mol] for ITCA 650 40 and 60 μg/day, respectively (P < 0.001 vs. placebo −0.1% [−1.3 mmol/mol]). In a prespecified analysis, greater HbA_{1c} reductions occurred in patients not receiving sulfonylureas (SUs) versus those receiving SUs (−1.7% vs. −1.2% [−18.6 and −13.1 mmol/mol]). At week 39, HbA_{1c} <7% [53 mmol/mol] was attained in 37%, 44%, and 9% of ITCA 650 40 μg/day, ITCA 650 60 μg/day, and placebo groups, respectively (P < 0.001 each dose vs. placebo). LS mean change from baseline body weight was −2.3 kg and −3.0 kg for ITCA 650 40 and 60 μg/day, respectively ($P \leq 0.015$ vs. placebo −1.0 kg). Nausea was the most common adverse event (AE) and subsided over time. Discontinuation for gastrointestinal AEs occurred in 7.2% with ITCA and 1.3% with placebo. Most AEs associated with procedures to place and remove ITCA 650 were mild and transient.

CONCLUSIONS

ITCA 650 significantly reduced HbA_{1c} and weight compared with placebo and was well tolerated in patients with uncontrolled type 2 diabetes on oral antidiabetes medications.

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Although numerous drugs are available for individualized management of type 2 diabetes, poor treatment adherence, suboptimal efficacy, inadequate weight control, and unacceptable tolerability remain barriers to glycemic control (1–3). Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) are considered effective therapeutic agents for the treatment of type 2 diabetes (4) that lower glucose, promote weight loss, and have a low risk of hypoglycemia (5) due to their glucose-dependent effect on insulin secretion (6). However, the need to administer these drugs by injection and low adherence and/or persistence to treatment are major barriers that have impeded the widespread use of the GLP-1 RA class.

Adherence to treatment with antidiabetes drugs is generally low and is reported to range from 38% to 54% with GLP-1 agonists in the U.S. (7,8). Qualitatively similar results have been shown in Europe (9). In addition to the negative impact on achieving effective glycemic control, poor medication adherence results in increased health care costs (1,2). Therefore, it stands to reason that in order to reduce the overall burden of diabetes, it is critical to address the issues of poor medication adherence.

ITCA 650 is an investigational combination drug-device product being developed for the treatment of type 2 diabetes (Supplementary Data). It consists of a small titanium matchstick-sized osmotic mini-pump that delivers a continuous subcutaneous infusion of exenatide for extended periods (10,11). Drug administration can be rapidly terminated if necessary by removing the ITCA 650 as exenatide levels fall rapidly within 24 h after removal (12). Placement and removal of ITCA 650 are performed by trained health care professionals in a brief office procedure. 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 and closed with Steri-Strips.

In a phase 2, randomized, 24-week, open-label, dose-ranging study, patients with type 2 diabetes inadequately controlled with metformin had significant reductions in HbA_{1c} and body weight at 24 weeks with ITCA 650 (13) that were maintained over 48 weeks of therapy (14). We report the FREEDOM-1 trial undertaken to investigate the efficacy and tolerability of two doses of ITCA 650 compared with placebo (osmotic mini-pump) over 39 weeks in patients with type 2 diabetes inadequately controlled on oral antidiabetes drugs.

RESEARCH DESIGN AND METHODS

The study was approved by an institutional review board and conducted in accordance with the Declaration of Helsinki and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines for Good Clinical Practice. All patients gave written informed consent. This study was registered at ClinicalTrials.gov (identifier NCT01455857). 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 pancreatitis events in a blinded manner. Investigative site personnel were provided with a kit 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

FREEDOM-1 was a randomized, double-blind, placebo-controlled, phase 3 study conducted at 126 clinical sites in the U.S. The study consisted of a 4-week screening period, a 39-week treatment period, and a 4-week posttreatment follow-up period.

Eligible patients were randomized in a 1:1:1 ratio to ITCA 650 40 μg/day, ITCA 650 60 μg/day, or placebo. Randomization to treatment groups and assignment of study devices was done via a central system. Treatment was initiated with the subdermal placement in the abdominal wall of either the introductory 20 μg/day dose of ITCA 650 or a matching placebo mini-pump. The mini-pumps were removed and replaced at week 13 with either 40 or 60 μg/day of ITCA 650 or ITCA 650 placebo for the subsequent 26 weeks (see Supplementary Data for description of placement procedure). All mini-pumps were removed at week 39.

Patient Selection

Patients with type 2 diabetes receiving stable (≥3 months) treatment with diet and exercise alone or with metformin (≥1,500 mg/day), sulfonylureas (SUs) (greater than or equal to half maximal dose), or pioglitazone ≥30 mg/day monotherapy or in any combination were eligible if they were 18 to 80 years old, had an HbA_{1c} ≥7.5% and ≤10% [58 to 86 mmol/mol], fasting plasma glucose (FPG) ≤270 mg/dL [15 mmol/L], BMI ≥25 to ≤45 kg/m^2, and serum calcitonin <50 ng/L at screening. Patients were excluded if they previously received a GLP-1 RA; took dipeptidyl peptidase 4 inhibitors, α-glucosidase inhibitors, meglitinides, sodium–glucose cotransporter 2 inhibitors, or insulin (except short-term treatment) within 3 months of screening; or had an estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m^2.

Patients were required to maintain their baseline dose of background medication throughout the study. Investigators were allowed to 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 rescue was required if the HbA_{1c} was >8% [63.9 mmol/mol] (see Supplementary Data for rescue criteria). Insulin glargine titrated to target FPG was recommended for rescue; however, oral antidiabetes medication could be added instead at the discretion of the investigator. Dipeptidyl peptidase 4 inhibitors, incretin mimetics, and sodium–glucose cotransporter 2 inhibitors were not allowed for rescue therapy.

Study Assessments

Blood samples were collected at prespecified time points and analyzed at the certified central laboratory (Quintiles Laboratories, Ltd., Marietta, GA) to determine levels of HbA_{1c}, FPG, fasting lipids (total cholesterol [TC], LDL cholesterol [LDL-C], HDL cholesterol [HDL-C], triglycerides, apolipoprotein B-100), adiponectin, insulin, and hs-CRP. 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 examination.

The primary study 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]. Changes in FPG, blood pressure (BP), lipids, and the percentage of patients requiring rescue were assessed. Safety end points included AEs, vital signs, electrocardiogram, and clinical laboratory findings. Antiexenatide antibodies (ADA) were determined in human serum samples using a validated enzyme-linked immunosorbent assay (Charles River Laboratories, formerly WIL Research, Skokie, IL). If samples were positive for ADA, neutralizing antibodies (Eurofins) and cross-reactivity of ADAs to GLP-1 and glucagon were determined. Hypoglycemia was defined as minor if symptoms were accompanied by a self-monitored plasma glucose <60 mg/dL (<3.3 mmol/L). A major event was defined as a hypoglycemic episode requiring the assistance of a third party to actively administer resuscitative measures (see Supplementary Data for hypoglycemia criteria).

Statistical Methods

The sample size was determined to demonstrate superiority of ITCA 650 60 μg/day versus placebo or ITCA 650 40 μg/day versus placebo with regard to change from baseline in HbA_{1c} after 39 weeks of treatment using a two-sided test. Based on the assumptions of an advantage of 0.7% [−7.7 mmol/mol] in HbA_{1c} reduction for each treatment group compared with placebo, an SD of 1.25, and a dropout rate of up to 30%, the sample size of 150 per group was required to achieve 97% power at a significance level of 0.025 for each comparison.

The safety population included all randomized patients who had a procedure started for the initial ITCA 650/placebo placement. The modified intent-to-treat (mITT) population included all patients from the safety population who had a valid baseline and at least one postbaseline HbA_{1c} value. All safety analyses were based on the safety population, and all efficacy analyses were based on the mITT population. The statistical analyses were performed with a significance level of 5% (two-sided). For the primary and secondary efficacy analyses, missing values were imputed using the last observation carried forward (LOCF) method with data postrescue excluded.

The efficacy-evaluable (EE) population included the patients in the mITT population who did not require rescue therapy and who had no major protocol deviations through week 39. All members of the EE population had baseline and week 39 HbA_{1c} values. Sensitivity analyses on change from baseline HbA_{1c}, change from baseline body weight, and HbA_{1c} <7% at week 39 were performed based on the EE population.

For the primary analysis, each ITCA 650 treatment group was compared with placebo based on an ANCOVA model with change in HbA_{1c} at LOCF end point as the outcome variable, treatment, baseline HbA_{1c}, and concomitant use of SUs as explanatory factors. Sensitivity analyses included a fixed-effects repeated measures ANCOVA model with the change in HbA_{1c} as the outcome variable and treatment, visit, baseline HbA_{1c}, SU use, and treatment by visit interaction as explanatory variables. The correlation of the repeated measures was modeled with a first order autoregressive covariance structure. The analysis of the secondary end point on change from baseline in weight at LOCF end point was performed similar to the primary analysis. A sensitivity analysis was performed using the repeated measures on change from baseline body weight similar to the repeated measures for HbA_{1c} with baseline HbA_{1c} covariate replaced with baseline body weight (see Supplementary Data for rescue criteria). For the analysis of secondary end point on proportion of patients with HbA_{1c} <7% [53 mmol/mol], each ITCA 650 treatment group was compared with placebo based on a logistic regression model with proportion of patients with HbA_{1c} <7% [53 mmol/mol] at LOCF end point as the outcome variable, treatment, baseline HbA_{1c}, and concomitant use of SUs as explanatory factors. A post hoc evaluation was conducted of the composite end point of at least a 1% reduction in HbA_{1c} and a 3-kg reduction in body weight. All other analyses presented here were prespecified in the statistical analysis plan.

A gatekeeping strategy was used to maintain type I error at $\alpha = 0.05$ across the family of primary and secondary analyses as specified above in a hierarchical order. First, both comparisons on primary end point were tested at $\alpha = 0.025$ level. These two comparisons acted as parallel gatekeepers for the secondary comparisons with $\alpha = 0.025$ for each dose versus placebo; that is, no secondary comparisons could be done unless at least one of the ITCA 650 doses was significantly superior to placebo in reducing HbA_{1c}.

Additional analyses included change from baseline in FPG, systolic and diastolic BP, and lipid parameters of TC, LDL-C, or HDL-C. The number of rescued patients was also summarized. All safety end points were provided with descriptive statistics only.

RESULTS

Four hundred and sixty patients were randomized, and 441 (95.9%) were included in the mITT population (Supplementary Fig. 1). Study completion rates were 79.9%, 78.4%, and 80.4% in the placebo, ITCA 650 40 μg/day, and ITCA 650 60 μg/day groups, respectively. Discontinuation for AEs occurred in 11.8% of patients treated with ITCA 650 40 μg/day, 7.8% with ITCA 650 60 μg/day, and 3.2% with placebo. Treatment groups were comparable at baseline for demographic and patient characteristics (Table 1). The mean duration of type 2 diabetes was 8.9 years, and mean HbA_{1c} was 8.5% [69.2 mmol/mol]. No differences were noted between treatment groups with respect to antidiabetes medications taken at baseline. Most patients (85.2%) were taking metformin, either as monotherapy (41.3%) or in combination with an SU (41.3%) (Table 1). The median dose of metformin was 2,000 mg/day. Approximately 11% of patients were managing their diabetes with diet and exercise alone.

Efficacy

The least squares (LS) mean change in HbA_{1c} from baseline to week 39 was significantly ($P < 0.001$) greater for each dose of ITCA 650 (40 μg/day −1.1% [−12.2 mmol/mol] and 60 μg/day −1.2% [−13.2 mmol/mol]) compared with placebo (−0.1% [−1.3 mmol/mol]). The LS mean difference was −1.0% (97.5% CI −1.3; −0.7) (−10.9 mmol/mol [95% CI −13.7; −8.2]) for 40 μg/day versus placebo ($P < 0.001$) and −1.1% (97.5% CI −1.4; −0.8) (−11.9 mmol/mol [95% CI −14.6; −9.2]) for 60 μg/day versus placebo ($P < 0.001$). At week 39, mean (SD) HbA_{1c} was 7.4 (1.1), 7.3 (1.1), and 8.4 (1.3) in the ITCA 650 40 μg/day, ITCA 650 60 μg/day, and placebo groups, respectively. The mixed-effect model with repeated measures (MMRM) sensitivity analysis was consistent with the primary analysis; the LS mean change in HbA_{1c} from baseline to week 39 was significantly ($P < 0.001$) greater for each dose of ITCA 650 (40 μg/day −1.2%

Table 1—Baseline demographic and clinical characteristics—safety population

Characteristic	ITCA 650 40 μg/day (*n* = 153)	ITCA 650 60 μg/day (*n* = 153)	Placebo (*n* = 154)
Age, years	55.5 ± 10.3	54.7 ± 9.6	54.7 ± 9.1
Female sex	64 (41.8)	62 (40.5)	62 (40.3)
Race			
White	129 (84.3)	125 (81.7)	126 (81.8)
Black or African American	20 (13.1)	21 (13.7)	23 (14.9)
Other	4 (2.6)	7 (4.6)	5 (3.3)
Hispanic or Latino	56 (36.6)	47 (30.7)	59 (38.3)
Duration of diabetes, years	9.1 ± 6.2	8.9 ± 6.9	8.6 ± 6.0
Body weight, kg	96.8 ± 18.6	97.6 ± 18.3	98.2 ± 21.9
BMI, kg/m^2	33.1 ± 5.1	33.8 ± 5.2†	33.7 ± 5.5
HbA_{1c}, % [mmol/mol]	8.5 ± 0.8 [69.5 ± 8.5]	8.5 ± 0.8 [68.8 ± 8.6]	8.5 ± 0.8 [69.9 ± 9.1]
FPG, mmol/L (mg/dL)	11.0 ± 2.7 (198.2 ± 48.6)	10.3 ± 2.6 (185.6 ± 46.8)	10.9 ± 2.8 (196.4 ± 50.5)
eGFR, mL/min/BSA	86.5 ± 19.2	87.6 ± 17.6	89.3 ± 19.2
Heart rate, bpm	74.9 ± 10.0	75.3 ± 10.0	74.7 ± 10.9
Systolic BP, mmHg	133.9 ± 14.6	131.6 ± 14.4	132.7 ± 15.1
Diastolic BP, mmHg	81.0 ± 8.7	80.5 ± 8.3	81.0 ± 8.5
Medications at baseline†	137 (89.5)	135 (88.2)	138 (89.6)
Metformin monotherapy	63 (41.2)	61 (39.9)	66 (42.9)
SU monotherapy	7 (4.6)	7 (4.6)	2 (1.3)
Metformin + SU	61 (39.9)	65 (42.5)	64 (41.6)
Metformin + SU + TZD	4 (2.6)	1 (0.7)	6 (3.9)

Data are mean ± SD or *n* (%). BSA, body surface area; TZD, thiazolidinedione. †One (0.7%) patient in the ITCA 650 60 μg/day group was taking TZD + metformin as background therapy.

[−13.1 mmol/mol] and 60 μg/day −1.2% [−13.4 mmol/mol]) compared with placebo (−0.2% [−1.7 mmol/mol]) (Supplementary Table 1). Significant reductions in HbA_{1c} from baseline were observed by week 6 and at each subsequent study time point for both ITCA 650 doses ($P < 0.001$ vs. placebo) (Fig. 1*A*).

Patients treated with ITCA 650 who were not receiving an SU as part of their antidiabetes regimen at baseline had greater reductions in HbA_{1c} at week 39 compared with those whose regimen included an SU (Fig. 1*B*). While a reduction in SU dose to prevent hypoglycemia was allowed per protocol, this only occurred in 9 (4.2%), 8 (3.8%), and 5 (2.4%) patients on ITCA 650 60 μg/day, ITCA 650 40 μg/day, and placebo, respectively.

Across all treatment groups, there were greater HbA_{1c} (mean ± SD) decreases from baseline in the subgroup with higher (>8.5% [69.4 mmol/mol]) baseline (40 μg/day −1.9% ± 1.0% [−20.8 ± 10.9 mmol/mol]; 60 μg/day −2.0% ± 1.0% [−21.9 ± 10.9 mmol/mol]; placebo −0.7% ± 1.8% [−7.7 ± 19.7 mmol/mol]) compared with the group with baseline HbA_{1c} ≤8.5% (40 μg/day −1.1% ± 1.0% [−12.0 ± 10.9 mmol/mol]; 60 μg/day −1.0% ± 1.0% [−10.9 ± 10.9 mmol/mol]; placebo −0.25% ± 1.0% [−2.7 ± 10.9 mmol/mol]). In both ITCA 650 groups, patients in the EE population achieved a mean HbA_{1c} reduction of 1.4% ± 1.0% [15.3 ± 10.9 mmol/mol] compared with 0.4% ± 1.4% [4.4 ± 15.3 mmol/mol] in patients on placebo.

The estimated mean change in body weight from baseline was significantly greater for ITCA 650 40 μg/day (−2.3 kg) and 60 μg/day (−3.0 kg) compared with placebo (−1.0 kg; $P = 0.015$ and $P < 0.001$ vs. placebo, respectively) (Fig. 1*C*). The estimated treatment difference in weight was −1.3 kg (97.5% CI −2.4; −0.1) for 40 μg/day versus placebo and −2.0 kg (97.5% CI −3.1; −0.8) for 60 μg/day versus placebo. An MMRM sensitivity analysis of weight was consistent with the primary analysis (Supplementary Table 2).

At week 39, a dose-dependent and significantly greater proportion of patients in the ITCA 650 groups achieved HbA_{1c} <7% [53 mmol/mol] (37% and 44% vs. 9%; $P < 0.001$ for 40 μg/day and 60 μg/day, respectively, vs. placebo) and HbA_{1c} <6.5% [47.5 mmol/mol] (22% and 33% vs. 6%; $P = 0.062$ for 40 μg/day and $P < 0.001$ for 60 μg/day vs. placebo).

Significant reductions in FPG were observed for each dose of ITCA 650 versus placebo ($P < 0.001$). The LS mean difference from placebo was −2.4 mmol/L (95% CI −3.1; −1.7) and −2.1 mmol/L (95% CI −2.8; −1.4) for ITCA 650 40 and 60 μg/day, respectively. Significantly ($P < 0.001$) fewer patients required rescue therapy in the ITCA 650 treatment arms (40 μg/day [15.6%] and 60 μg/day [11.3%]) versus the placebo group (39.2%) (Supplementary Fig. 2). The median number of days to first rescue treatment was 191 days and 186 days with ITCA 650 40 and 60 μg/day, respectively, and 148 days with placebo. The majority of ITCA 650–treated patients who received rescue did so at weeks 27–33 compared with the placebo group where patients were primarily rescued at weeks 18–22.

An exploratory evaluation of the composite end point of reduction in HbA_{1c} and body weight at least 1% and 3 kg, respectively, demonstrated a dose-dependent increase in the proportion of patients achieving the composite end point at week 39: 46% with ITCA 650 60 μg/day, 34% with ITCA 650 40 μg/day, and 16% with placebo (Fig. 2).

Small improvements in lipid parameters (TC, LDL-C, or HDL-C) were observed, but there were no significant differences between ITCA 650 treatment groups and placebo at week 39 (Supplementary Table 3) with the exception of a significant decrease in triglycerides with ITCA 650 60 μg/day ($P = 0.029$ vs. placebo).

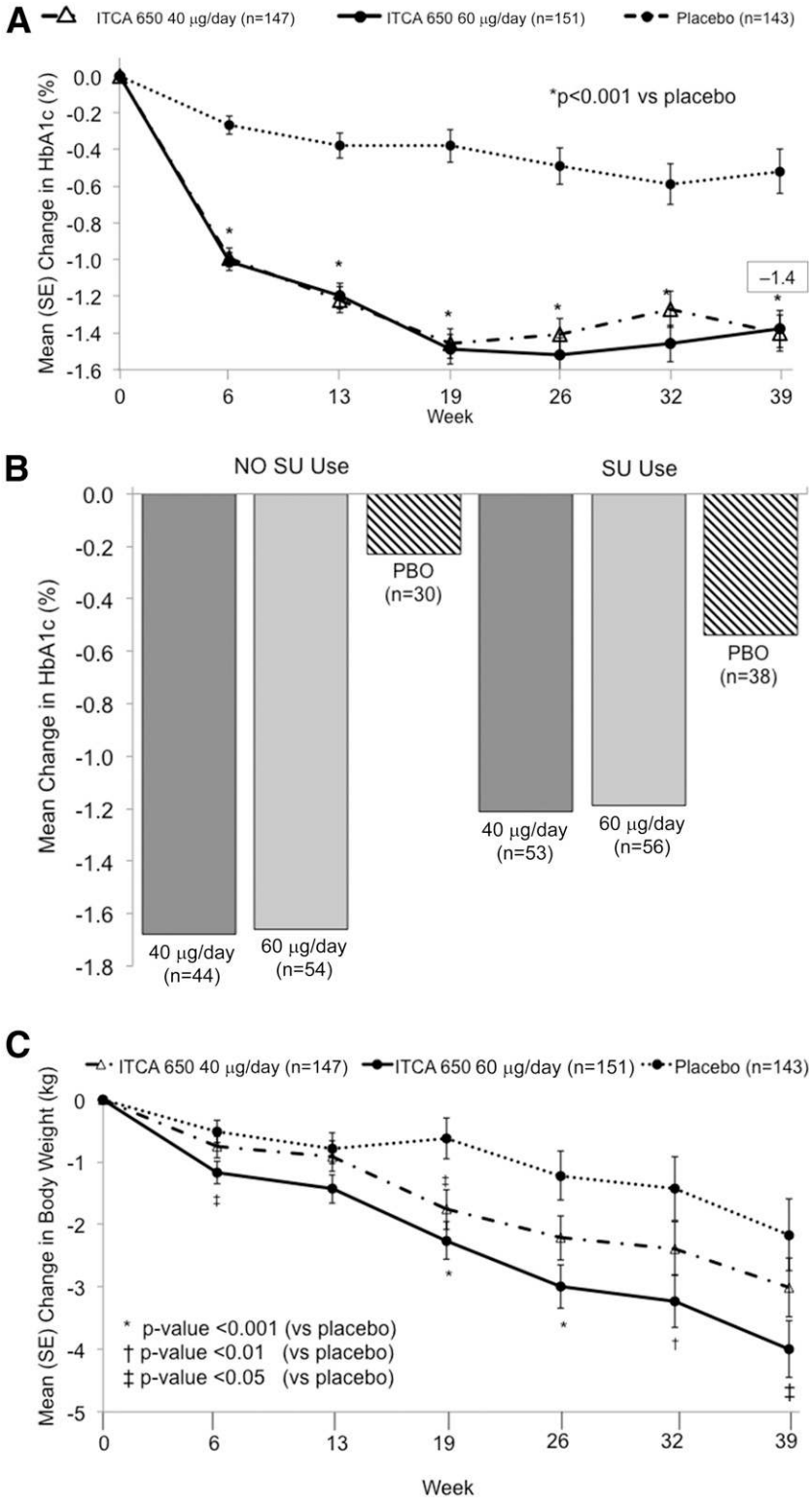

Figure 1—*A*: Mean change from day 0 to week 39 for HbA_{1c} for the primary mITT analysis. *B*: Mean change for HbA_{1c} at week 39 by background SU use. *C*: Mean change from day 0 to week 39 in body weight. *$P < 0.001$; †$P < 0.01$; ‡$P < 0.05$ for ITCA 650 60 μg/day vs. placebo (PBO).

Mean systolic BP decreased in each ITCA 650 treatment group (−3.7 and −1.3 mmHg, ITCA 40 μg/day and ITCA 60 μg/day, respectively), while the placebo group had a slight increase in mean systolic BP (0.8 mmHg). Only the decrease in systolic BP in the ITCA 650 40 μg/day group was significant compared with placebo (P = 0.010). Mean diastolic BP decreased slightly in each treatment group; however, there were no significant changes observed versus placebo (−0.7 and −0.3 vs. −0.2 mmHg for ITCA 650 20/40 and 20/60 μg/day, respectively, vs. placebo) (Supplementary Table 3). A modest increase in heart rate was seen in the ITCA 650 treatment groups compared with placebo (ITCA 650 40 μg/day = 4.0 bpm and ITCA 650 60 μg/day = 4.1 bpm vs. placebo = 1.2 bpm) (Supplementary Table 5).

Tolerability

The proportion of patients who reported at least one AE was 82.4% and 85.0% for ITCA 650 40 and 60 μg/day, respectively, and 71.4% for placebo (Supplementary Table 4). A total of 32 serious AEs (7.3%) were reported and were evenly distributed across the three treatment groups with respect to incidence and type of event. Discontinuation due to AEs occurred in 18 (11.8%) patients with ITCA 650 40 μg/day, 13 (8.5%) with ITCA 60 μg/day, and 6 (3.9%) with placebo. Gastrointestinal disorders (nausea, vomiting, and diarrhea) were the most common AEs leading to discontinuation, occurring in 7.2%, 7.2%, and 1.3% of patients, respectively (Supplementary Fig. 1). The most common AEs in the ITCA 650 treatment groups were nausea, vomiting, and diarrhea. The majority were mild or moderate in severity. The incidence of nausea and vomiting was similar for both doses: highest early in the first week after treatment initiation and dose escalation and then decreased toward baseline for the remaining study intervals (Fig. 3). Cholelithiasis was reported in one patient each in the ITCA 650 40 μg/day and placebo groups.

Minor hypoglycemic events occurred in 9.2% and 6.5% of patients treated with ITCA 650 40 and 60 μg/day, respectively, and 2.6% with placebo. The majority (89%) of events occurred in patients receiving SU therapy. No major hypoglycemic events were reported.

The incidence of any AE occurring at the site of placement/removal of the ITCA 650 or placebo device was low and similar across the treatment groups. Because all patients received a study device and the incidence of AEs was similar, the events were combined. The most frequently reported AEs related to the administration site were site bruises, mild bleeding, and minor pain with an incidence of 3.9–4.6%. The incidence of superficial skin infection

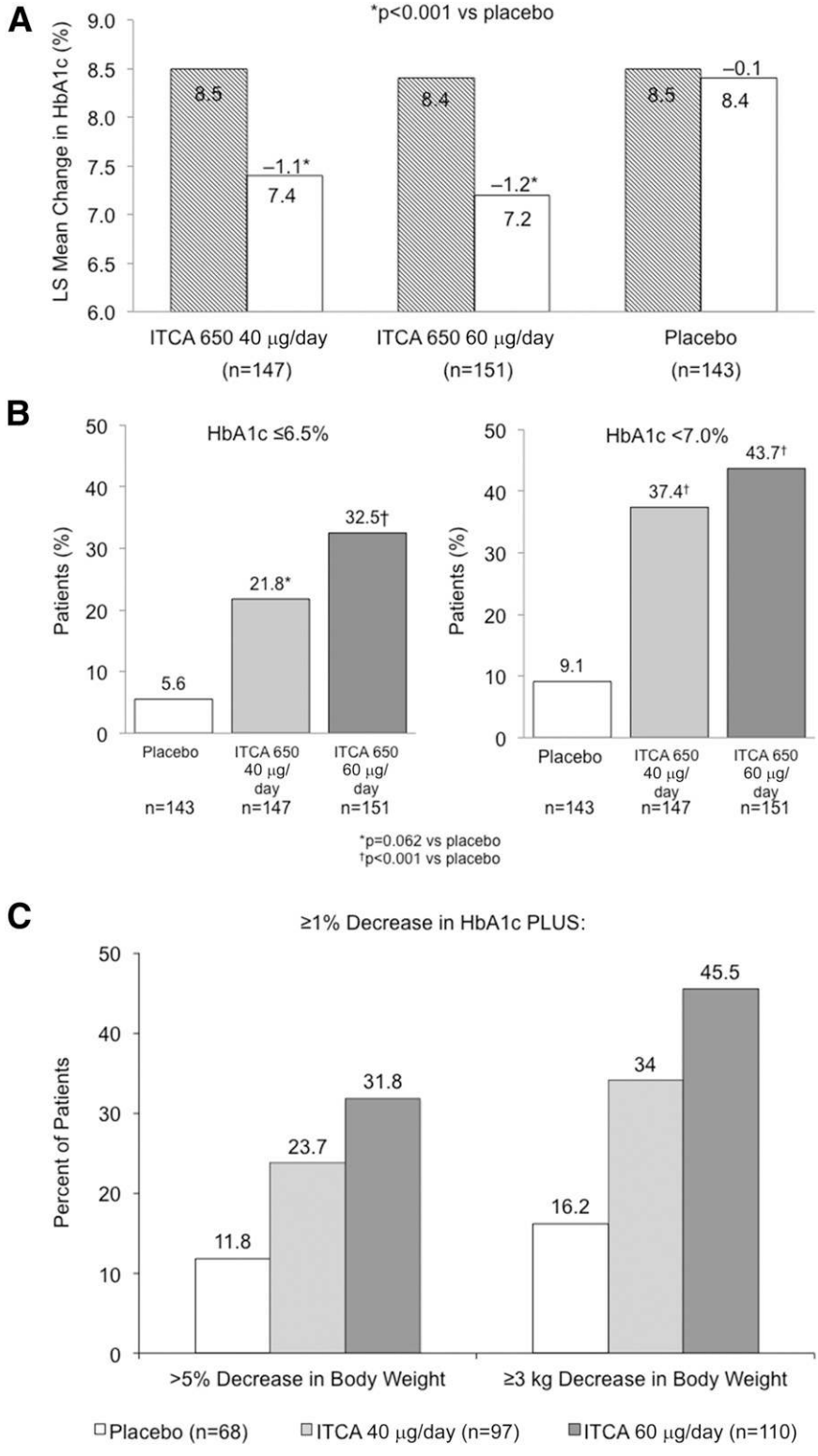

Figure 2—*A*: LS mean change in HbA_{1c} (%) from baseline. *B*: Proportion of patients achieving goal HbA_{1c} at week 39. *C*: Proportion of patients achieving at least a 1% decrease in HbA_{1c} and weight loss of at least 3 kg or >5% decrease at week 39. PLUS indicates that the values are HbA_{1c} + either of the weight groups.

was low (1.3%). Most of these events were mild and transient. There were 1,321 study procedures performed. A small percent (3.33%) of removals were not successful at first attempt (reported as "device removal failed") primarily due to the device being placed too deeply in the subcutaneous tissue. Twenty-six (3.0%) patients required referral to a specialist and had a successful removal of the device during an outpatient visit. Most events were considered mild in severity and did not result in discontinuation of the patient from the study.

Two deaths (worsening of chronic obstructive pulmonary disease [placebo] and hypoxemic respiratory failure [ITCA 650 40 μg/day]) occurred during the trial. Neither was considered related to study treatment. No pancreatitis or thyroid cancer was reported.

Amylase and lipase levels were comparable at baseline across treatment groups. No notable changes from baseline in amylase levels were observed in the ITCA 650 groups compared with placebo. A small increase in median lipase levels was observed at week 39 for the ITCA 650 groups compared with placebo (Supplementary Table 5) but was still within normal range and did not correlate with clinical signs or symptoms.

Positive ADA levels were detected in 24.5% of patients treated with ITCA 650. The incidence was similar between ITCA 650 doses and declined over time. The incidence of cross-reactivity to glucagon and/or GLP-1 was 12% and also diminished over time. The presence of antiexenatide or cross-reactive antibodies did not impact the response to treatment (HbA_{1c}) or the incidence of AEs.

CONCLUSIONS

In this 39-week, phase 3 study, statistically and clinically meaningful improvements in HbA_{1c}, body weight, and the proportion of patients achieving goal HbA_{1c} <7% [53 mmol/mol] were demonstrated with two doses of ITCA 650 versus placebo. These results are consistent with an open-label phase 2 study of ITCA 650 that demonstrated significant efficacy of these two doses over 24 weeks (13) and are comparable to those reported with exenatide and other GLP-1 agonists (15). Significantly fewer patients in the ITCA 650 groups (11–16%) required rescue therapy for hyperglycemia compared with patients in the placebo group (~40%). Rescue in the ITCA 650 groups occurred later (primarily at weeks 27–33) compared with placebo (at weeks 18–22 for majority of patients), driven largely by the rescue requirement for HbA_{1c} to be ≤8% [63.9 mmol/mol] by week 26.

While the reduction in HbA_{1c} was similar between the two doses of ITCA 650, the

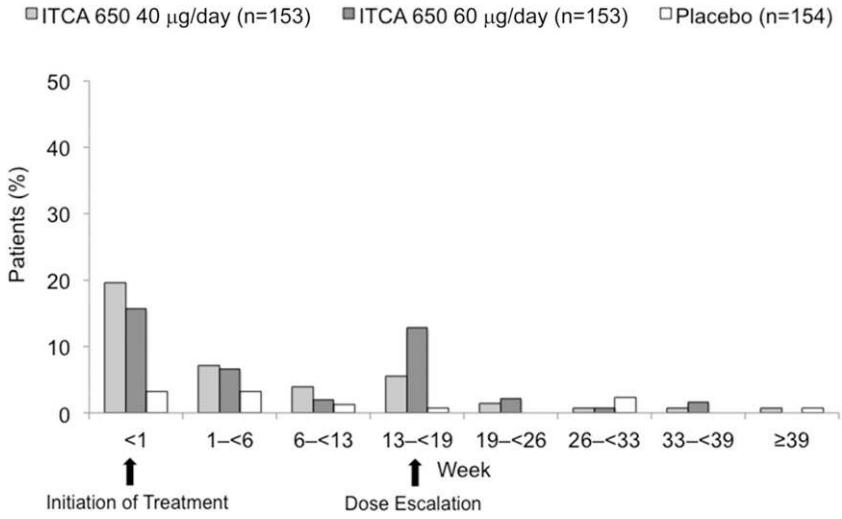

Figure 3—Incidence of nausea over time from day 0 to week 39.

60 μg/day dose demonstrated greater overall efficacy (aggregate of HbA_{1c} reduction, weight loss, goal attainment of HbA_{1c} <7% and ≤6.5%, need for rescue) without a dose-dependent increase in AEs compared with the 40 μg/day dose. These results are consistent with the findings of a previous study comparing exenatide 0.8 and 2 mg once weekly (16) and support the observation that HbA_{1c} and weight reductions may be optimized at different doses with GLP-1 agonists.

Treatment with ITCA 650 was generally well tolerated. Nausea was the most common AE, usually occurring at the time of treatment initiation and dose escalation and returning to baseline in subsequent weeks. Discontinuation due to nausea was low and not dose dependent. The incidence reported in this study was comparable to the incidence reported with other GLP-1 RAs (17,18).

The procedures to administer ITCA 650 are simple and performed during an outpatient office visit by trained medical personnel that include physician assistants and nurse practitioners. Procedures were well tolerated by patients. AEs reported at the site of administration were generally mild in severity and self-limited. A small number of removal procedures required referral to specialty health care providers and resulted in successful removals. Enhanced training and the introduction in latter ITCA 650 studies of a depth guide that limits the depth of placement to the subdermis has significantly reduced the likelihood of placement in the subcutaneous fat.

The study population had long-standing poorly controlled diabetes despite a majority (~90%) being on stable treatment with oral antidiabetes medications. Intensification of treatment for patients with type 2 diabetes is often delayed for years despite poor glycemic control on one or more oral antidiabetes drugs (19,20). Clinical inertia and/or poor treatment adherence delay the appropriate advancement of effective therapy and result in frequent treatment discontinuations or nonpersistence (21). Evidence from controlled trials demonstrates that earlier intensification is superior to sequential add-on therapy for achieving glycemic control (22,23).

GLP-1 RAs are broadly recommended as add-on to monotherapy with metformin or in combination with multiple oral agents and insulin for patients with poorly controlled diabetes (21,24). In this study, greater efficacy was observed in the subgroup of patients who were not receiving an SU. These patients were predominantly receiving drug treatment with metformin. Since effectiveness with exenatide is not expected to wane over time (25) and adherence to treatment is expected while ITCA 650 is in situ, early addition to metformin monotherapy is considered the optimal treatment scenario with ITCA 650.

The strengths of this study include the use of a double-blind, randomized, placebo-controlled design with all patients undergoing the procedures to place and remove the mini-pump and the comprehensive analysis of safety and tolerability. Once ITCA 650 is placed, no action is required on the part of the patient beyond standard attention to lifestyle management in order to ensure therapeutic adherence for the 3- or 6-month dosing period. The 39-week duration is longer than many studies in a type 2 diabetes population, but owing to the chronic nature of the disease, longer duration studies will address the durability of effect with ITCA 650.

Poor medication adherence to antidiabetes drugs and lack of persistence are major obstacles to effective glycemic control (2,7). The potential for complete adherence to treatment when the ITCA 650 is in place addresses a key challenge that has profound implications for patients, health care professionals, and payers. Although a small proportion of patients are unable to tolerate their treatment and discontinue therapy due to side effects, those who remain on ITCA 650 were ensured to receive continuous subcutaneous exenatide for the full duration of the treatment period.

ITCA 650 is the first injection-free GLP-1 RA. This integrated drug-device combination maintains long-term effective blood concentrations of exenatide and has the ability to ensure medication adherence and lead to sustained glycemic control and weight loss. This report provides the first results from a large controlled study that demonstrates the efficacy and tolerability of ITCA 650 in patients with long-standing type 2 diabetes on a variety of background antidiabetes medications.

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