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ITCA 650 Improves Glycemic Control and Reduces the Need to Advance Antidiabetes Therapy

Robert Henry, MD;[1] Brian Schwartz, MD;[2] Lise Kjems, MD, PhD;[2] Holly Huang, PhD;[2] Michelle Baron, MD[2]

[1]University of California and VA San Diego Healthcare System, San Diego, CA; [2]Intarcia Therapeutics, Inc., Boston, MA

Brian Schwartz, MD
Intarcia Therapeutics Inc.
brian.schwartz@intarcia.com

ABSTRACT

Background: ITCA 650, an osmotic mini-pump in development for T2D, continuously delivers exenatide SC for up to 6 months after subdermal placement. Significant reductions in HbA1c and weight occurred in 2 clinical trials: FREEDOM-1, a 39-week, placebo-controlled trial in pts on OADs and FREEDOM-2, a 52-week, study of ITCA 650 vs sitagliptin (SITA) in pts uncontrolled on metformin. Advancement of antidiabetes therapy (AT), a meaningful measure of the effectiveness and sustainability of antidiabetes therapy was evaluated for the pooled populations of these trials.

Methods: Combined data from 814 uncontrolled T2D pts on OADS (414 on ITCA 650, 257 on sitagliptin, 143 on placebo) was analyzed for AT. Mean baseline HbA1c was 8.6%. Data for ITCA 20 mcg/day for 13 weeks, then 60 mcg/day were pooled (n=413). AT, the addition of or increase of therapy from baseline, was protocol mandated based on predefined criteria. AT was required after Week 26 for HbA1c >8%.

Results: The majority of ITCA 650 treated pts achieved and maintained glycemic control below the threshold for AT. An increase in AT occurred in all groups at Week 26 but 88% of ITCA 650 pts remained on assigned therapy at Week 39. In contrast, there was a progressive increase in the need for AT in the placebo and SITA groups after Week 26.

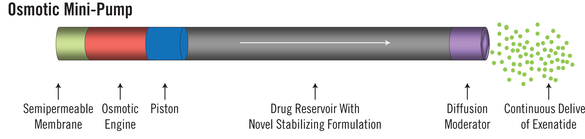
Conclusions: In uncontrolled T2D, ITCA 650 results in significantly improved and stable glycemic control without AT in the majority of patients.

INTRODUCTION

- Type 2 diabetes is the most prevalent chronic disease in the U.S. as well as in many countries of the world.
- Patients with type 2 diabetes frequently require advancement of therapy beyond initial metformin treatment to achieve treatment goals.
- Although numerous drugs are available for the individualized management of type 2 diabetes, poor treatment adherence, sub-optimal efficacy, inadequate weight control, and unacceptable tolerability remain barriers to optimal glycemic control.[1-3]
- GLP-1 receptor agonists are effective therapeutic agents for the treatment of T2D; the need to administer by injection may limit their use early in treatment.
- Adherence to treatment with antidiabetic drugs is generally low, and is reported to range from 38% to 54% with GLP-1 receptor agonists.[4]
- In addition to the negative impact on achieving effective glycemic control, poor medication adherence results in increased healthcare costs.[1,2]
- ITCA 650 is an investigational drug device combination product that consists of an osmotic mini-pump (**Figure 1**) that provides continuous subcutaneous (SC) delivery of exenatide for up to 6 months after its subdermal placement in the abdominal wall.
- Placement and removal of ITCA 650 is performed by trained healthcare professionals in a brief office procedure. The sterile mini-pump is placed in the sub-dermis of the abdominal wall using a placement tool and is removed or replaced through a small (~5 mm) incision and closed with Steri-Strips.
- Exenatide plasma levels are maintained as long as the ITCA 650 device is in situ, and no action is required on the part of the patient.
- In patients with type 2 diabetes, Phase 3 studies with ITCA 650 demonstrated significant improvement in change from baseline HbA1c, body weight, and HbA1c<7% compared with placebo or sitagliptin.[5,6]

[NEW LINK TO BE PROVIDED]

Figure 1. ITCA 650 Osmotic Mini-Pump



- ITCA 650 releases drug at a predetermined rate based on osmosis. Extracellular fluid enters through the semi-permeable membrane directly into the osmotic engine (salt gradient). The resulting pressure pushes the piston at a slow and consistent rate of travel and forces the drug formulation to be released through the orifice of the diffusion moderator.

OBJECTIVE

- The need to advance therapy, a meaningful measure of the effectiveness and sustainability of antidiabetes therapy, was evaluated for ITCA 650 vs. sitagliptin and placebo using data from 2 randomized, controlled studies (Baron et al, 2015; Rosenstock et al, 2016).

METHODS

- This post hoc analysis was based on pooled data from 2 randomized, double-blind, double-dummy Phase 3 studies from the FREEDOM Program, evaluating ITCA 650 for the treatment of T2D (**Table 1**).
- Descriptive statistics on disposition, demographic and baseline characteristics of patients who needed to advance antidiabetes therapy were compared to the overall patient population.

Table 1. Description of Efficacy Studies Included in the FREEDOM Program

Study	Baseline Anti-DM Therapy	Duration	No. of Randomized Patients	Treatments
FREEDOM-1	Diet + exercise or oral antidiabetic drugs	39 weeks	460	ITCA 650 20/40 or 20/60 mcg/d vs. placebo
FREEDOM-2	Metformin	52 weeks	535	ITCA 650 20/60 vs. sitagliptin 100 mg

- Combined data from 814 patients with T2D uncontrolled on oral antidiabetes drugs (413 on ITCA 650, 257 on sitagliptin, 143 on placebo) were analyzed for the proportion of patients who needed to advance their antidiabetes therapy.
  - Data were analyzed up to Week 39
- Data for the dosing regimen of ITCA 20 mcg/day (for 13 weeks) followed by 60 mcg/day for 26 weeks were pooled (n=413).
- Advancement of antidiabetes therapy (AT), the addition of or increase in therapy, was protocol mandated based on predefined criteria:
  - Day 0 to Week 13:
    - Two or more fasting self-monitored blood glucose (SMBG) values >240 mg/dL during any 7-day period
    - Two consecutive FPG values >240 mg/dL
  - After Week 13:
    - Two or more fasting SMBG values >200 mg/dL during any 7-day period;
    - Two consecutive FPG values >200 mg/dL
  - An HbA1c elevation of ≥1.5% at any timepoint in the study
  - An HbA1c >8.0% after Week 26
- Data were analyzed for the modified intent-to-treat population (mITT), which included all patients who initiated study treatment (had a procedure started for placement of ITCA 650/ITCA placebo or received sitagliptin or placebo) and who had a valid baseline and at least 1 post baseline HbA1c value.

RESULTS

- ITCA 650 significantly reduced HbA1c and body weight compared to placebo and sitagliptin (**Table 2**) and was well tolerated in patients with poorly controlled T2DM taking oral antidiabetes medications.

Table 2. LS Mean Change From Baseline to Endpoint in FREEDOM-1 and FREEDOM-2 (mITT Population)

	LS Mean (standard error)		
	ITCA 650 60 mcg/d	Placebo	Sitagliptin
FREEDOM-1 39 weeks *P*<0.001 vs. placebo*	-1.2 (0.09) (n=151)	-0.1% (0.09) (n=143)	Not applicable
FREEDOM-2 52 weeks *P*<0.001 vs. sitagliptin**	-1.47 (0.08) (n=263)	Not applicable	-0.76% (0.08) (n=257)

* Least-squares means were from an ANCOVA model with the change in HbA1c at LOCF Endpoint as the outcome variable and treatment, baseline HbA1c (%) and sulfonylureas stratification based on randomization as explanatory variables.

**The comparison (2-sided p-value) of ITCA 650 versus sitagliptin was based on LS means from a repeated measures model with each post-baseline visit treated as equally spaced repeated measures and an unstructured matrix describing the covariance between measurements taken at different visits. Treatment, visit and the interaction between treatment and visit were included as fixed effects and baseline HbA1c as the covariate

- AT occurred in 11.8%, 25.7%, and 39.2% of patients treated with ITCA 650, sitagliptin, and placebo respectively.
- Ninety-one percent (91.1%) of patients who advanced therapy completed the studies.
- At baseline, demographic and clinical characteristics of patients who advanced therapy and the overall mITT Populations were comparable (**Table 3**).

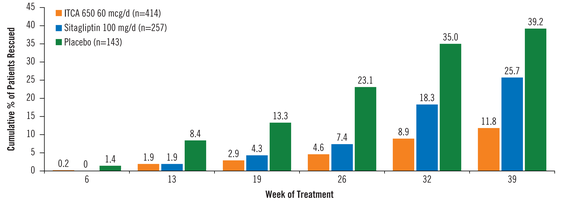
Table 3. Baseline Demographic and Clinical Characteristics for the Advancing Therapy Population vs. Overall Study – mITT Population

	Advancing Therapy Population			Overall mITT Population		
	ITCA 650 20/60 mcg/d	Sitagliptin 100 mg/d	Placebo	ITCA 650 20/60 mcg/d	Sitagliptin 100 mg/d	Placebo
Number	56	91	56	414	257	143
Age, years[a]	53.7 ± 9.5	54.7 ± 10.0	55.4 ± 8.9	55.1 ± 9.7	54.6 ± 10.3	55.0 ± 9.1
Female, %	43%	48%	43%	44%	41%	41%
Race, (%)						
White	82.1%	78.0%	82.1%	78.0%	76.7%	83.2%
Black/African American	12.5%	14.3%	12.5%	12.3%	12.5%	13.3%
Other	5.4%	7.7%	5.4%	9.7%	10.8%	3.5%
Time since diabetes diagnosis (years)[a]	8.5 ± 5.6	8.2 ± 5.4	7.3 ± 5.5	8.8 ± 6.4	7.4 ± 5.3	9.7 ± 6.1
Body weight, kg[a]	93.7 ± 20.2	91.2 ± 20.0	99.7 ± 21.7	94.2 ± 19.5	92.0 ± 21.4	97.3 ± 21.6
BMI, kg/m^2 [a]	33.0 ± 5.6	32.7 ± 5.7	34.2 ± 5.6	33.1 ± 5.5	32.4 ± 5.6	33.6 ± 5.5
HbA1c (%)[a]	9.0 ± 1.0	8.9 ± 0.9	8.8 ± 0.8	8.5 ± 0.9	8.7 ± 0.9	8.5 ± 0.8

[a]Mean, standard deviation

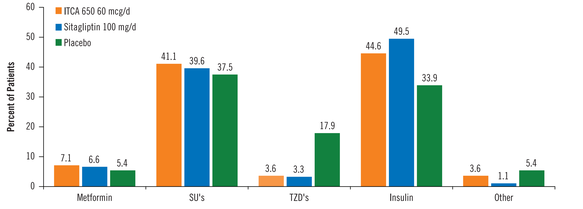
- The majority of ITCA 650 treated patients who advanced therapy achieved and maintained glycemic control below the threshold (**Figure 2**).
- An increase in the incidence of patients advancing therapy occurred in all groups at Week 26.
- Approximately 88% of ITCA 650 patients remained on assigned therapy at Week 39 and did not need additional therapy.
- Cumulatively, 26% of sitagliptin and 39% of placebo treated patients needed to advance therapy by Week 39.
- A progressive increase in the incidence of patients advancing therapy was observed in the sitagliptin and placebo groups after Week 26 as the criteria became more stringent.

Figure 2. Percent of Patients Who Advanced Therapy by Week of Treatment



- Generally, sulfonylureas and insulin were used most often to advance therapy and was comparable between groups with the notable exception of more TZD use in the placebo group. (**Figure 3**).

Figure 3. Medications Used for Advancing Therapy by Treatment Group



DISCUSSION

- In this analysis of patients who were poorly controlled on optimal doses of antidiabetic drugs, greater efficacy (HbA1c, weight, and goal attainment) was achieved with ITCA 650 compared to sitagliptin and placebo.
- By Week 39 approximately 26% and 40% of patients in the sitagliptin and placebo treatment groups respectively needed to advance therapy compared with 12% of patients receiving ITCA 650.
- The need to advance therapy with sitagliptin or placebo was incremental and progressive over time compared to ITCA 650.
- This is consistent with the sustained efficacy of ITCA 650 observed over time.

CONCLUSION

- In this analysis of 2 randomized, controlled studies in patients with inadequately controlled type 2 diabetes, add-on therapy with ITCA 650 20/60 mcg/d significantly improved glycemic control without the need for advancement of antidiabetic therapy in most patients.

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