A Randomized, Double-Blind, Placebo-Controlled, 39 Week Trial of ITCA 650 as Add-on Therapy in Type 2 Diabetes

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Disclosures

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L. Kjems: Employee; Intarcia Therapeutics, Inc.

Global Impact of Type 2 Diabetes

- IDF estimates that in 2011, >360 million people worldwide had diabetes and this number will grow to 550 million by 2030.\(^1\)
  - In the EU alone, 43 million are projected to have diabetes by 2030.\(^2\)
- In Europe, 37% of patients are not at goal.\(^3,4\)
- Costs for T2DM in Europe are estimated at €90 billion annually.\(^5\)
- Medication adherence represents a major challenge; WHO estimates that 50% of patients are adherent to chronic medications, including OADs.\(^6\)
- Annual cost of medication nonadherence is €125 billion in the EU.\(^7\)
- Only two-thirds of patients with T2DM in the EU are adherent to medication, resulting in poor glycemic control, increased morbidity and mortality, and greater costs.\(^3,4,8-10\)
- A critical need exists for medical technology that is more effective and maintains glycemic control by optimizing adherence and persistence.

Background on Intarcia Delivery Technology

Osmotic Mini-Pump

Semipermeable Membrane  Osmotic Engine  Piston  Drug Reservoir with Novel Stabilizing Formulation  Diffusion Moderator  Continuous Delivery of Exenatide

Mini-Pump Size of a Matchstick

✓ Sub-dermal placement once/twice yearly
✓ Done in a brief, in-office, sterile procedure by MD or NP/PAs
✓ Similar procedures are reimbursed in many countries

Continuous Delivery of Exenatide In Vitro

✓ Continuous zero order delivery for up to a full 12 months
✓ Novel formulation stabilizes peptides at body temps for years
ITCA 650

- ITCA 650, currently in phase 3 development, represents the first once or twice-yearly injection-free delivery of a GLP-1 RA
  - ITCA 650 subcutaneous osmotic mini-pumps are designed to consistently deliver exenatide over 6 or 12 months

- In Phase 2, ITCA 650 significantly reduced HbA1c over 48 weeks in metformin-treated subjects; baseline HbA1c of ~8%
  - HbA1c reduction of -1.4%
  - 3-4 kg weight loss
  - Well tolerated and low discontinuation rates

- ITCA 650 combines the potential of 100% adherence with improved efficacy for treating T2DM
A Phase 3, randomized, double-blind, placebo-controlled, multi-center study; treatment duration was 39 weeks: randomized

Objective: evaluate the efficacy, safety and tolerability of ITCA 650 in patients with type 2 diabetes (T2DM)
Study Design

Phase 3 Randomized, Double-Blind, Placebo-Controlled, Multicenter 39-Week Study

Inclusion Criteria
✓ T2DM age 18 to 80 years
✓ HbA1c ≥ 7.5% and ≤10.0%
✓ Diet and exercise alone and/or MET, SU or TZD monotherapy or any combination of the three
✓ BMI 25 – 45 kg/m²

Screening

Initial Treatment 13 Weeks
- ITCA 650 20 mcg/d
- ITCA 650-20 mcg/d
- ITCA 650 Placebo

Uptitrated Treatment 26 Weeks
- ITCA 650 60 mcg/d
- ITCA 650 40 mcg/d
- ITCA 650 Placebo

Follow-up

Weeks
0 13 39 43
Study Outcomes

◆ Primary Efficacy Measure
  ✓ HbA1c changes with ITCA 650 40 and 60 mcg/day vs placebo

◆ Secondary Outcome Measures
  ✓ Body weight changes with ITCA 650 40 and 60 mcg/day vs placebo
  ✓ Attainment of target HbA1c <7%

◆ Other Outcome Measures
  ✓ FPG changes with ITCA 650 40 and 60 mcg/day vs placebo
  ✓ Lipid profile changes
  ✓ Blood pressure (systolic, diastolic) changes
  ✓ Need for rescue therapy within the 39 week treatment period

◆ Safety Parameters of Interest
  ✓ GI adverse events, hypoglycemia, amylase, lipase, calcitonin, immunogenicity, ECGs, vital signs
## Baseline Characteristics and Demographics

<table>
<thead>
<tr>
<th>Parameters</th>
<th>ITCA 650 40 mcg/day (N=153)</th>
<th>ITCA 650 60 mcg/day (N=153)</th>
<th>Placebo (N=154)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55±10</td>
<td>55±10</td>
<td>55±9</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>89 (58.2)</td>
<td>91 (59.5)</td>
<td>92 (59.7)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>33.1±5.1</td>
<td>33.8±5.2</td>
<td>33.7±5.5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>96.8±18</td>
<td>97.6±18.3</td>
<td>98.2±22</td>
</tr>
<tr>
<td>Duration of Diabetes (years)</td>
<td>9.1±6.2</td>
<td>8.9±6.9</td>
<td>8.6±6.0</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.5±0.8</td>
<td>8.5±0.8</td>
<td>8.5±0.8</td>
</tr>
<tr>
<td>FPG (mmol/L)</td>
<td>11±2.7</td>
<td>10.3±2.6</td>
<td>10.7±2.8</td>
</tr>
<tr>
<td>eGFR (mL/min)</td>
<td>86±9</td>
<td>88±18</td>
<td>89±19.2</td>
</tr>
<tr>
<td>Diet and Exercise, n (%)</td>
<td>16 (10)</td>
<td>18 (12)</td>
<td>16 (10)</td>
</tr>
<tr>
<td>Metformin, n (%)</td>
<td>63 (41)</td>
<td>61 (40)</td>
<td>66 (43)</td>
</tr>
<tr>
<td>SU + Metformin, n (%)</td>
<td>61 (40)</td>
<td>65 (42)</td>
<td>64 (42)</td>
</tr>
</tbody>
</table>

a mean±SD unless otherwise noted
Patient Disposition

Patients Screened
n=1466

Patients Randomized
n=460

Screen Failures (n=1006)
- Inclusion/Exclusion Criteria (551)
- Lab abnormality (177)
- Other reasons (218)
- Enrolled in HBL substudy (60)

ITCA 650
40 mcg/day
n=147
Completed 120 (78.4%)
Discontinued 33 (21.6%)
Withdrawal 12 (7.8%)
Adverse event 18 (11.8%)
Lost to follow-up 1 (0.7%)
Other 2 (1.3%)

ITCA 650
60 mcg/day
n=151
Completed 123 (80.4%)
Discontinued 30 (19.6%)
Withdrawal 12 (7.8%)
Adverse event 12 (7.8%)
Loss of control 1 (0.7%)
Pregnancy 1 (0.7%)
Other 4 (2.6%)

Placebo
n=143
Completed 123 (79.7%)
Discontinued 31 (20.1%)
Withdrawal 15 (9.7%)
Adverse event 5 (3.2%)
Loss of control 2 (1.3%)
Lost to follow up 3 (1.9%)
Pregnancy 1 (0.6%)
Other 5 (3.2%)
HbA1c Changes at 39 Weeks (LOCF)

*p<0.001 vs. placebo

Baseline

Placebo
n=143
8.5% -0.1%

40 mcg/d
n=147
8.4% -1.1%

60 mcg/d
n=151
8.5% -1.2%

Week 39
HbA1c Changes According to SU Treatment

**Placebo**

All Pts: -1.4%

**ITCA 60 mcg dose**

mITT Population
HbA1c Changes According to SU Treatment

- Placebo: -1.4%
- Prior SU: -1.2%
- No SU: -1.7%
- All Pts: -1.4%

mITT Population
HbA1c Targets Attained at Study Endpoint

Placebo (n=143) | 40 mcg/d (n=147) | 60 mcg/d (n=153)

* p<0.001 vs. placebo
** p=0.062 vs. placebo

mITT Population
Body Weight Changes at Week 39

mITT Population

- Placebo: -1.0 kg
- 40 mcg/d: -2.3 kg*
- 60 mcg/d: -3.0 kg**

* p<0.015 vs. placebo
** p<0.001 vs. placebo
Progressive Weight Loss Over 39 Weeks

Mean Change From Baseline in Body Weight (kg)

- ITCA 650 40 mcg/d (n=147)
- ITCA 650 60 mcg/d (n=151)

* P<0.001 vs placebo
† P<0.01 vs placebo
‡ P<0.05 vs placebo

mITT Population

Week
Composite Outcome of HbA1c and Weight Reductions

≥1% Decrease in HbA1c PLUS:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo</th>
<th>40 mcg/d</th>
<th>60 mcg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5% Decrease in Body Weight</td>
<td>6%</td>
<td>17%</td>
<td>21%</td>
</tr>
<tr>
<td>≥3 kg Decrease in Body Weight</td>
<td>18%</td>
<td>34%</td>
<td>47%</td>
</tr>
</tbody>
</table>

mITT Population
## Adverse Events of Special Interest

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>ITCA 650 40 mcg/day (n=153)</th>
<th>ITCA 650 60 mcg/day (n=153)</th>
<th>Placebo (n=154)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Treatment-Emergent Adverse Event</td>
<td>126 (82.4%)</td>
<td>130 (85.0%)</td>
<td>110 (71.4%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>47 (30.7%)</td>
<td>48 (31.4%)</td>
<td>15 (9.7%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>29 (19.0%)</td>
<td>37 (24.2%)</td>
<td>3 (1.9%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>22 (14.4%)</td>
<td>19 (12.4%)</td>
<td>15 (9.7%)</td>
</tr>
<tr>
<td>Hypoglycemia (minor only)</td>
<td>14 (9.2%)</td>
<td>10 (6.5%)</td>
<td>4 (2.6%)</td>
</tr>
<tr>
<td>Application Site / Procedure AEs</td>
<td>54 (35.3%)</td>
<td>50 (32.7%)</td>
<td>44 (28.6%)</td>
</tr>
<tr>
<td>Any Serious AEs</td>
<td>9 (5.9%)</td>
<td>6 (3.9%)</td>
<td>5 (3.2%)</td>
</tr>
<tr>
<td>Any AEs Leading to Discontinuation</td>
<td>18 (11.8%)</td>
<td>13 (8.5%)</td>
<td>6 (3.9%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (2.6%)</td>
<td>5 (3.3%)</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (2.0%)</td>
<td>5 (3.3%)</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (1.3%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Procedure and Application site</td>
<td>6 (3.9%)</td>
<td>0</td>
<td>2 (1.3%)</td>
</tr>
</tbody>
</table>
Nausea Incidence

% of Patients

Week

<1 1 – <6 6 – <13 13 – <19 19 – <26 26 – <33 33 – <39 ≥39

Placebo 20/40 mcg/d 20/60 mcg/d

Initial Mini-pump

Higher Dose Mini-pump
Summary

◆ Efficacy
  ✓ ITCA 650 resulted in meaningful reductions in HbA1c of 1.4% with associated weight loss and even greater reductions of 1.7% in those not taking an SU

◆ Safety Profile
  ✓ Safety profile was consistent with reported data for exenatide and GLP-1 receptor agonist class with low rate of discontinuation for nausea and vomiting (2%-3.3%), which was similar between ITCA 650 groups
  ✓ Administration site events were generally mild, transient, and expected from any minor procedure (temporary bruising, irritation, hematoma, etc)
  ✓ Anti-exenatide antibodies detected in 25% of ITCA 650 patients decreased over time and did not impact efficacy or AEs

◆ ITCA 650 Dosing Regimen
  ✓ While FREEDOM-1 was not designed to compare active doses, 60 mcg/d was consistently better than 40 mcg/d for key efficacy parameters without a trade-off in tolerability
Conclusion

- ITCA 650, an injection-free osmotic mini-pump placed in the sub-dermis to deliver continuous subcutaneous exenatide

- ITCA 650 resulted in meaningful reductions in HbA1c and body weight over 39 weeks in inadequately controlled patients with type 2 diabetes
Investigators

Corey Anderson; Stephen Aronoff; Samir Arora; Timothy Barker; Jill Beavins; Gary Bedel; Ramon Berenguer; Thomas Blevins; John Buse; David Butuk; Robert Buynak; Deanna Cheung; James Clower; Lisa Cohen; Jonathan Condit; Lisa Connery; Richard Cook; Eva-Maria Heurich; Raymond De la Rosa; Wasim Deeb; Douglas Denham; Donna DeSantis; Richard Egelhof; David Ensz; Naynesh Patel; Richard Glover; Sinikka Green; Carl Griffin; Charles Herring; Darrell Herrington; Carlton Thomas; John Finney; John Joseph; Mario Juarez; John Kessel; Rachel Kientcha; Stephanie Kinnaman; Leslie Klaff; Elias Kolettis; Sam Lerman; Kathryn Lucas; Lon Lynn; Adonis Maiquez; Earl Martin; Michael Winnie; Robert McNeill; Purvi Mehra; Francisco Miranda; Abel Murillo; Samer Nakhle; Joel Neutel; Eugene Pampe; Rakesh Patel; Daniel Pomposini; George Raad; Vanita Aroda; Marc Rendell; Steven Reynolds; Ernie Riffer; Jeffrey Rosen; Julio Rosenstock; Jeffrey Rothman; Khalid Saeed; Carolyn Maldonado-Garcia; Jay Sandberg; Scott Segel; Jean-Louis Selam; Gerald Shockey; Timothy Smith; Ronald Stegemoller; Mimi Van Der Leden; Carl Vance; Jorge Venereo; Aaron Vinik; Larry Watkins; Mark Christiansen; Kate Wheeler; Jonathan Wilson; Peter Winkle; Jonathan Wise; Mary Carroll; Tina Thethi; Ron Hsieh; Mohammed Allaw; William Seger; Rica Stamatin; Erich Schramm; Danny Sugimoto; Rafael Canadas; Gregory Gottschlich; Carl Meisner; Aron Schlau; Eugene Soroka; Jose Bautista; Louis Chaykin; Angela Adelizzi; Alan Cohen; Alan Forker; Christopher Sorli; Steven Zeig; Ankur Doshi; Carol Wysham; Lana Law; Frederick Jenkin; Andres Patron; James Capo; William Byars; Gregory Flippo; Gregory Funk; Michael Goldstein; Mark Kutner; Derek Lewis; Cristian Breton; Mark Turner; Steven Barag; Victor Elinoff; Michael Sanson; Philip Raskin; Brad Frandsen; Timothy Howard; Darron Molter; Jung Oh; John Pullman; Brian Snyder; Robert Lipetz