Efficacy of ITCA 650 vs Sitagliptin in Uncontrolled Type 2 Diabetes on Metformin: The FREEDOM-2 Randomized Double-Blind 52-Week Study

Julio Rosenstock; Douglas Denham; Prakash Prabhakar; Rehan Azeem; Lise Kjems; Michelle Baron
For the FREEDOM 2 Study
Disclosures

Julio Rosenstock, MD

▪ Research Support:
  Merck, Pfizer, Sanofi, Novo Nordisk, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, AstraZeneca, MannKind, Lexicon, Janssen, Daiichi Sankyo, Intarcia, Hanmi and Boehringer Ingelheim

▪ Advisory Boards, Consulting Honorarium:
  Merck, Novo Nordisk, Sanofi, Eli Lilly, Daiichi Sankyo, Astra Zeneca, Intarcia, Alere, Janssen and Boehringer Ingelheim
Study Background

- Most Type 2 DM remain inadequately controlled due in part to:
  - Progressive nature of the disease
  - Limitations of current glucose-lowering agents and treatment regimens
  - Clinical inertia
  - Poor adherence and persistence with therapies over time

- ITCA 650 is the first injection-free delivery of a GLP-1 Receptor Agonist
  - ITCA 650 is an osmotic mini-pump, which is designed to deliver subcutaneous (SC) Exenatide consistently after subdermal placement every 6 or 12 months
Study Background on Intarcia Delivery Technology

Mini-Pump Size of a Matchstick!

✓ 4 mm x 44 mm size
✓ Subdermal placement once/twice yearly
✓ Placement during a quick, in-office, sterile procedure by MD or NP/PAs
✓ Approved reimbursement codes for similar procedures in the U.S.

Osmotic Mini-Pump

- Semipermeable Membrane
- Osmotic Engine
- Piston
- Drug Reservoir with Novel Stabilizing Suspension
- Diffusion Moderator
- Immediate Release Exenatide

Continuous Subcutaneous Exenatide with ITCA 650 vs Sitagliptin in Type 2 DM on Metformin
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Study Background on Intarcia Delivery Technology

Delivery of Exenatide 60 mcg/d For 1 Year

**In Vitro Assay at 37°C**

- **12-Month In Vitro Release Testing Shows Consistent Zero Order Delivery**
  - Novel formulation stabilizes peptides at body temperatures for years
  - Amount of drug released is determined by validated HPLC method
  - In Vitro testing performed at human body temperature
  - Consistent release rate observed at target for 12-month ITCA 650 mini-pump

Yang B et al. Diabetes Technology Meeting; November 8-10, 2012; Bethesda, MD
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- FREEDOM-1 in uncontrolled T2DM on OADs (HbA1c 8.5%) over 39 weeks
  - HbA1c reductions of -1.4% and up to -1.7% in mainly Metformin-treated
  - Body weight loss of ~3 kg
  - Well tolerated and low discontinuation rates

To Demonstrate the Efficacy and Safety of 52 Weeks of ITCA 650 vs Sitagliptin in Reducing HbA1c in Type 2 DM on Metformin
Continuous Subcutaneous Exenatide with ITCA 650 vs Sitagliptin in Type 2 DM on Metformin

Study Design

Phase 3 Randomized, Double-Blind, Placebo-Controlled, Multicenter 39-Week Study
N=535 on Metformin Monotherapy

**Screening**

**Initial Dose**
13 Weeks
- ITCA 650--20 mcg/d
  - Oral Placebo
- Sitagliptin 100 mg/d
  - ITCA 650--Placebo

**Change to Higher Dose**

**Maintenance Dose**
39 Weeks
- ITCA 650--60 mcg/d
  - Oral Placebo
- Sitagliptin 100 mg/d
  - ITCA 650--Placebo

**Follow-up**
4 Weeks

**Inclusion Criteria**
- T2DM age 18 to 80 years
- HbA1c ≥ 7.5% to ≤10.5%
- Metformin ≥ 1500 mg/d
- BMI 25 – 45 kg/m²
Continuous Subcutaneous Exenatide with ITCA 650 vs Sitagliptin in Type 2 DM on Metformin

Study Outcomes Over Time and at Week 52

- **Primary Efficacy Endpoint**
  - HbA1c changes

- **Secondary Endpoints**
  - Proportion with a decrease in HbA1c >0.5% and ≥2 kg weight loss
  - Body weight changes
  - Proportion of HbA1c <7%

- **Other Outcome Measures**
  - FPG
  - Lipids
  - BP
  - Need for rescue therapy

- **Safety Parameters of Interest**
  - GI adverse events, hypoglycemia, lipase, calcitonin, immunogenicity
Continuous Subcutaneous Exenatide with ITCA 650 vs Sitagliptin in Type 2 DM on Metformin

Patient Disposition

Patients Screened
N=1299

Randomized
N=535

ITCA 650 60 mcg/d
N=268

Discontinued 61 (22.8%)
✓ Withdrawal by patient 18 (6.7%)
✓ Adverse event 31 (11.6%)
✓ Lost to follow-up 16 (6.0%)
✓ Loss of control 3 (1.1%)
✓ Other 9 (3.4%)

Sitagliptin 100 mg/d
N=267

Discontinued 48 (18.0%)
✓ Withdrawal by patient 21 (7.9%)
✓ Adverse event 10 (3.7%)
✓ Loss to follow up 16 (6.0%)
✓ Loss of control 4 (1.5%)
✓ Other 12 (4.5%)
Continuous Subcutaneous Exenatide with ITCA 650 vs Sitagliptin in Type 2 DM on Metformin

**Baseline Characteristics**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>ITCA 650 60 mcg/day N=265</th>
<th>Sitagliptin 100 mg/day N=265</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age years, mean ± SD</td>
<td>55.4 ± 9.8</td>
<td>54.6 ± 10.3</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>145 (55)</td>
<td>158 (60)</td>
</tr>
<tr>
<td>BMI kg/m², mean ± SD</td>
<td>32.8 ± 5.6</td>
<td>32.5 ± 5.6</td>
</tr>
<tr>
<td>Diabetes Duration, mean ± SD</td>
<td>8.8 ± 6.1</td>
<td>7.8 ± 5.4</td>
</tr>
<tr>
<td>HbA1c %, mean ± SD</td>
<td>8.6 ± 0.9</td>
<td>8.7 ± 0.9</td>
</tr>
<tr>
<td>eGFR mL/min/BSA, mean ± SD</td>
<td>87 ± 19</td>
<td>88 ± 18</td>
</tr>
<tr>
<td>Metformin Monotherapy</td>
<td>265 (100%)</td>
<td>264 (99.9%)</td>
</tr>
</tbody>
</table>
Continuous Subcutaneous Exenatide with ITCA 650 vs Sitagliptin in Type 2 DM on Metformin

FPG Changes at Week 52

-47* LS Mean FPG (mg/dL)

ITCA 60 mcg/d vs Sitagliptin 100 mg/d

*p<0.001 vs Sitagliptin

mITT Population
Continuous Subcutaneous Exenatide with ITCA 650 vs Sitagliptin in Type 2 DM on Metformin

HbA1c Changes Over Time and at 52 Weeks

mITT Population

ITCA 650 60 mcg/d
Sitagliptin 100 mg/d

LS Mean Final HbA1c
ITCA 650 = 7.1%
Sitagliptin = 7.8%

*<p<0.001 vs Sitagliptin

LS Mean Change in HbA1c (%)

Week

ITCA 650 60 mcg/d
Sitagliptin 100 mg/d

LS M Change in HbA1c (%)

-1.5%*
Continuous Subcutaneous Exenatide with ITCA 650 vs Sitagliptin in Type 2 DM on Metformin

Body Weight Changes Over Time and at 52 Weeks

-5.0  -4.0  -3.0  -2.0  -1.0  0.0
LS Mean Change in Weight (kg)

Week

ITCA 650 60 mcg/day
Sitagliptin 100 mg/day

-4.0*  92.2  92.0  -1.3
LS Mean Change in Body Weight (kg)

ITCA 650 60 mcg/d  N=263
Sitagliptin 100 mg  N=257

* p<0.001 vs Sitagliptin

mITT Population
Continuous Subcutaneous Exenatide with ITCA 650 vs Sitagliptin in Type 2 DM on Metformin

Composite Reductions HbA1c >0.5% and Weight Loss ≥2 kg

**Week 52**

![Graph showing change in body weight and HbA1c](image)

- **ITCA 60mcg (n=171)**
- **Sitagliptin 100mg (n=126)**

* 61% / 28%

* Percentage of patients at Week 52 who achieved a reduction in HbA1c of >0.5% and weight loss of ≥2 kg from baseline

**Odds Ratio = 3.63**

p < 0.001 vs. sitagliptin

**mITT Population**
Continuous Subcutaneous Exenatide with ITCA 650 vs Sitagliptin in Type 2 DM on Metformin

HbA1c Targets Attained at Week 52

- ITCA 650 60 mcg/d (n=171): 61%
- Sitagliptin 100 mg (n=126): 42%

P<0.001

mITT Population
## Continuous Subcutaneous Exenatide with ITCA 650 vs Sitagliptin in Type 2 DM on Metformin

### Adverse Events of Special Interest

<table>
<thead>
<tr>
<th>Any Treatment-Emergent Adverse Event</th>
<th>ITCA 650 60 mcg/d N=265</th>
<th>Sitagliptin 100 mg N=265</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>218 (82.3%)</td>
<td>198 (74.7%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>83 (31.3%)</td>
<td>36 (13.6%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>51 (19.2%)</td>
<td>14 (5.3%)</td>
</tr>
<tr>
<td>Hypoglycemia (mild)</td>
<td>30 (11.3%)</td>
<td>19 (7.2%)</td>
</tr>
<tr>
<td></td>
<td>11 (4.2%)</td>
<td>5 (1.9%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Procedures and Application Site</th>
<th>Incidence (% of Total Procedures)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruising</td>
<td>0.36%</td>
</tr>
<tr>
<td>Hematoma</td>
<td>0.20%</td>
</tr>
<tr>
<td>Bleeding</td>
<td>0.61%</td>
</tr>
<tr>
<td>Infection</td>
<td>0.46%</td>
</tr>
<tr>
<td>Pain</td>
<td>0.82%</td>
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<thead>
<tr>
<th>Any Serious AE’s</th>
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<tr>
<td></td>
<td>15 (5.7%)</td>
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<tr>
<td></td>
<td>20 (7.5%)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Any AE’s Leading to Discontinuation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>33 (12.5%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14 (5.3%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (2.3%)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>2 (0.8%)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedure and Application Site</td>
<td>3 (1.1%)</td>
</tr>
<tr>
<td></td>
<td>5 (1.9%)</td>
</tr>
</tbody>
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Continuous Subcutaneous Exenatide with ITCA 650 vs Sitagliptin in Type 2 DM on Metformin

Nausea Incidence by Study Period

- Initial Dose: 20 mcg/d
- Escalation to: 60 mcg/d
- Replacement of 60 mcg/d device
Continuous SC delivery of Exenatide with ITCA 650 was meaningfully superior to Sitagliptin at 52 weeks for:

- Sustained reductions in HbA1c and body weight
- Composite of HbA1c and body weight Loss
- Proportion achieving HbA1c <7%

Administration site events were generally mild, transient, and consistent with those expected from any minor surgical procedure (temporary bruising, irritation, hematoma, etc)

Overall GI tolerability was consistent to what is known about Exenatide and the GLP-1 RA class
Continuous SC administration of Exenatide with ITCA 650 is a novel approach to improve glycemic control ensuring adherence and consistent delivery of therapy for 6 to 12 month periods for Type 2 Diabetes management!
Continuous Subcutaneous Exenatide with ITCA 650 vs Sitagliptin in Type 2 DM on Metformin

Investigators

Canada: Jeffrey Rubin; Richard Dumas; Karl Misik; Gregory Garrioch; Anil Gupta; Sam Henein; Randolph Hart; Petros Dzongowski; Guy Tellier

Croatia: Aleksander Knezevic; Miro Bakula; Ivan Gornik; Dubravka Dvorscak

Denmark: Annette Justesen; Jeppe Gram Torben Østergaard; Ulla Schmidt; Trine Christensen; Ole Svendsen

Germany: Dirk Hagemann; Gerhard Klausmann; Joachim Sauter; Markolf Hanefeld; Jochen Seufert; Bernhard Winkelmann; Reinhold Jerwan-Kelm; Ludger Rose

Israel: Eliezer Klainman; Ilana Harman-Boehm; Ofri Mosenzon; Mark Niven; Mazen Elia; Falad Adawi

Latvia: Valdis Pirags

Malaysia: Sree Kantan Nayar P.K.S. Nayar; Norhaliza Mohd Ali; Norasyikin Rahman; Izani Wan Mohd Wan Mohamed

Mexico: Jesus David Morales Cerda; Leobardo Valle Molina; Sigfrido Miracle Lopez; Norma Alicia Martinez Trezo; Cesar Gonzalo Calvo Vargas; Enrique Granados Reyes

Saudi Arabia: Hawazen Zarif

South Africa: Sumaya Hansa; Aysha Badat; Nazira Carrim-Ganey; Johannes Lombaard; Mohamed Mookadam; Margaretha Du Toit; Tasneem Vally; Graham Ellis; Mashra Gani; Asad Bhorat

United States: Robert Buynak; Mario Juaraz; Steven Reynolds; Carolyn Maldonado-Garcia; Samir Arora; Eval-Maria Heurich; Donna DeSantis; Michael Guice; Mark Jabro; Leslie Klaff; Earl Edward Martin; Abel Murillo; Kate Wheeler; EliEngel; David Klonoff; Danny Sugimoto; Aron Schlau; Christopher Sorli; Gregory Flippo; Mark Kutner; Richard Steward; Bryce Palchick; Douglas Young; Naveed Razzaque; Nabil Andrawis; David Francyk; Gary Bedel; Richard Egelhof; Naynesh Patel; Rachel Kientcha-Tita; Stephanie Kinnaman; Lon Lynn; Hitham Tayoun; Janet McGill; Francisco Miranda; Joel Neutel; Ronald Stegemoller; Mary Fiona Carroll; Dany Zayour; Eugene Soroka; Ankur Doshi; Frederick Jenkin; Don Fixler; Nashwa Gabra; David Butuk; Kathryn Lucas; Jeffrey Rosen; Jorge Venereoo; Mark Christiansen; Andres Patron; Philip Raskin; John Pullman; Michael Adams; Richard Lorraine; Neil Fraser; Samer Nakhle; Jay Sandberg; Carl Meisner; Douglas Logan; Jennefer Sutton; Hugo Toro; Deanna Cheung; Ernie Riffer; Julio Rosenstock; Michael Winnie; Lisa Connery; Douglas Denham; Gilbert Martinez; Ramon Berenquer

Thanks!