The GLP-1 Receptor Agonist Exenatide and its Effects in Type 2 Diabetes

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  - Investigator
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Overview of GLP-1 Receptor Agonists: Today and the Future

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Incretin Hormones

- Incretins are hormones secreted by intestinal endocrine cells in response to nutrient intake

- Incretins influence glucose homeostasis via multiple actions including glucose-dependent insulin secretion, postprandial glucagon suppression, and slowing of gastric emptying\(^1\)

- Incretins were identified when it was found that glucose given orally produced a greater stimulation of insulin release than when an equivalent glucose level was achieved by intravenous infusion\(^2\)
  - This well-described phenomenon is called the “incretin effect”
  - The incretin effect accounts for ~60% of total insulin release following a meal

Incretin Effect

**Incretin Effect**

The incretin effect is diminished in patients with type 2 diabetes (T2D).


*P<0.05; †Plasma
The Incretins GLP-1 and GIP

Two incretins are primarily responsible for the incretin effect:

- **Glucagon-like peptide 1 (GLP-1)**
  - Synthesized and released mostly from L cells located in ileum and colon\(^1,2\)
  - Multiple sites of action: pancreatic β and α cells, GI tract, CNS, and heart\(^3\)
  - Actions are receptor mediated\(^2,3\)
  - Secretion is impaired in T2D

- **Glucose-dependent insulinotropic polypeptide (GIP)**
  - Synthesised and released mostly from K cells of the duodenum and jejunum\(^1,2\)
  - Site of action: predominantly pancreatic β cells; also acts on adipocytes, neural progenitor cells, and osteoblasts\(^3,4\)
  - Actions are receptor mediated\(^2,3\)
  - In patients with T2D, levels of GIP are normal or even slightly increased, but its action is minimal\(^2\)

Postprandial GLP-1 Levels in T2D

![Graph showing postprandial GLP-1 levels in different glucose tolerance groups.]

Mean ± SE; N=102; *p<.05 between T2D and normal glucose tolerance groups; 1Plasma
GLP-1 Potentiates Glucose-induced Insulin Secretion

- **Potentiators**
  - ACh
  - CCK

- **Inhibitors**
  - Sulfonylureas
  - Epinephrine
  - Somatostatin
  - Galanin

- **Glucose to Insulin**
  - ATP
  - [Ca\(^{2+}\)]
  - Mitochondrial Metabolism
  - DAG
  - PKC
  - IP3
  - [Ca\(^{2+}\)] stores
  - PKA
  - cAMP
  - AC
  - Gs
  - Gi
  - Gq

- **Potentiators**
  - GLP-1
  - ACh
  - CCK

Created by Michael Trautmann, MD
GLP-1 Effects Are Glucose Dependent in T2D

N=10; Mean ± standard error of the mean; *p<.05; †Plasma
Tests were performed after an overnight fast.
Insulin Secretion During Euglycaemia and Hypoglycaemia

Mean Insulin Secretion Rates

Placebo  | Exenatide
---|---
5 mmol/L | 4 | 3.2 | Recovery

Mean (SE) Insulin Secretion Rate (pmol/min)

Mean (SE) Serum C-peptide Concentration (pmol/L)

N=11; SE = standard error
GLP-1 SC Injection
Slowed Gastric Emptying in T2D

SC Injection GLP-1 (1.5 nmol/kg)

Liquid Meal

Gastric Volume (mL)

Time (min)

SC = SC; Mean ± SEM; N=7; *p<.0001
GLP-1 ICV Suppresses Food Intake in 24-hour Fasted Rats

![Bar graph showing 2-hour food intake with GLP-1 ICV treatments]

*GLP-1 + Antagonist significantly different from GLP-1 (p<.01).

*ICV = intracerebroventricular

GLP-1 Activated β-Cell Neogenesis in a Rat Model of Diabetes

Untreated Diabetic Rats

Diabetic Rats Treated With GLP-1

Double immunostaining for BrdU and insulin (A and B) and indirect immunoperoxidase staining for insulin (C and D) in 7-day-old Rats

D = duct
Pancreatic islets cultured in the absence of GLP-1 lost organisation after 5 days.

By Day 5, 45% of islets in control cultures had lost their 3-D structure.

Only 15% of GLP-1–treated islets lost their 3-D structure in 5 days (p<.01 vs control).

GLP-1 Effects in Humans: Understanding the Glucoregulatory Role of Incretins

GLP-1 secreted upon the ingestion of food

Promotes satiety and reduces appetite

β cells: Enhances glucose-dependent insulin secretion

α cells: ↓ Postprandial glucagon secretion

Liver: ↓ Glucagon reduces hepatic glucose output

Stomach: Slows gastric emptying

β cells: Enhances glucose-dependent insulin secretion

↓ Beta-cell workload

Potential GLP-1 Effects in Humans

Heart:
- Cardioprotection
- Cardiac function

Muscle/Adipose:
- Glucose uptake and storage

Adapted from Baggio LL, Drucker DJ. Gastroenterology. 2007;132:2131-2157.
Cardiac Effects of GLP-1 in Patients with AMI and Left Ventricular Dysfunction

Mean Change (%) in LVEF

<table>
<thead>
<tr>
<th>LVEF (%)</th>
<th>Baseline</th>
<th>Post IV GLP-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>30 ± 5</td>
<td>45 ± 7</td>
</tr>
<tr>
<td>GLP-1</td>
<td>25 ± 4</td>
<td>50 ± 6</td>
</tr>
</tbody>
</table>

Mean Change in Regional Wall Motion Score

<table>
<thead>
<tr>
<th>ASE Regional Wall Motion Score</th>
<th>Baseline</th>
<th>Post IV GLP-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>GLP-1</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Mean ± SEM; Control Group, N=10; GLP-1 Group, N=11 AMI and LVEF <40% after successful primary angioplasty. AMI = acute myocardial infarction; ASE = American Society of Echocardiography; LVEF = Left ventricular ejection function.

Post IV GLP-1 = post 72-hour intravenous GLP-1 infusion.

Current GLP-1–based Approaches for Improving Glycaemic Control

- GLP-1 is extremely short-lived in human plasma\(^1\)
  - Active plasma half-life of \(~2\) minutes
  - Caused by degradation by dipeptidyl peptidase IV (DPP-4)
  - GLP-1 levels are reduced in T2D

- GLP-1–based approaches:
  - Agents that prolong the activity of endogenous GLP-1\(^1\)
    - DPP-4 inhibitors
      - Potential for additional immune-related effects
  - GLP-1 receptor agonists\(^1,2\)
    - DPP-4–resistant GLP-1 derivatives
      - GLP-1 analogs, albumin-bound GLP-1
    - Novel peptides that mimic the glucoregulatory actions of GLP-1
      - Exenatide

Exenatide (exendin-4)\(^1\)
- Synthetic version of salivary protein found in the Gila monster
- Approximately 50% identity with human GLP-1
  - Binds to known human GLP-1 receptors on β cells \textit{in vitro}
  - Resistant to inactivation by DPP-4

Acute Exenatide Infusion Restored First-Phase Insulin Response in Patients With T2D

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Mean (SE); N=25.
The Glucoregulatory Actions of Exenatide
Exenatide vs Sitagliptin MOA Study: Study Design

- Primary endpoint: comparison of the effects of exenatide and sitagliptin on 2-hour PPG concentrations in patients with T2D

MET background; MOA = mechanism of action; QAM = once per day in the morning; BID = twice daily; PPG = postprandial glucose
# Exenatide vs Sitagliptin MOA Study: Demographic and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Evaluable Patients (n = 61)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, Female/Male (%)</strong></td>
<td>54/46</td>
</tr>
<tr>
<td><strong>Age (y)</strong></td>
<td>54 ± 9</td>
</tr>
<tr>
<td><strong>Race, Caucasian/Black/Hispanic (%)</strong></td>
<td>30/8/62</td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td>167.0 ± 9.9</td>
</tr>
<tr>
<td><strong>Body weight (kg)</strong></td>
<td>91.5 ± 18.8</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>32.6 ± 5.1</td>
</tr>
<tr>
<td><strong>A1C (%)</strong></td>
<td>8.5 ± 1.2</td>
</tr>
<tr>
<td><strong>Duration of diabetes (y)</strong></td>
<td>7 ± 5</td>
</tr>
<tr>
<td><strong>Fasting triglycerides (mmol/L)</strong></td>
<td>1.9 ± 1.0</td>
</tr>
<tr>
<td><strong>FPG (mmol/L)</strong></td>
<td>9.9 ± 2.7</td>
</tr>
<tr>
<td><strong>2-hr PPG (mmol/L)</strong></td>
<td>13.6 ± 3.6</td>
</tr>
</tbody>
</table>

Patients with T2D; MET background; Mean ± SD, unless otherwise indicated; BMI = body mass index; FPG = fasting plasma glucose

**Plasma GLP–1 and Exenatide Levels**

Postprandial plasma levels of exenatide exceeded physiologic levels of GLP–1 in patients with T2D. Evaluable population, n=61 for all treatment groups; Mean \( \pm \) SE; 2-wk posttreatment concentration data. Adapted from DeFronzo RA, et al. *Curr Med Res Opin.* 2008;24:2943–2952.

**Graph Details**
- **X-axis**: Plasma GLP-1 and Plasma Exenatide
- **Y-axis**: 2-h Postprandial Plasma GLP-1 (pmol)
- **Data Points**:
  - Baseline: 7.2
  - Exenatide: 7.9, 15.1, 63.8
  - Sitagliptin: 63.8

Patients with T2D; Evaluable population, n=61 for all treatment groups; Mean \( \pm \) SE; 2-wk posttreatment concentration data.
Exenatide Reduced PPG Concentrations to a Greater Extent Than Sitagliptin

Patients with T2D; Evaluable population, n = 61 for all treatment groups; Mean ± SE; * least square (LS) mean ± SE, P<0.0001
Greater Insulin Release With Exenatide Than With Sitagliptin

Insulinogenic index = \frac{\text{increment in plasma insulin}^*}{\text{increment in plasma glucose}^*}

*increment was defined as the post-meal minus the pre-meal levels at the time of peak glucose concentration

Patients with T2D; Evaluable population, n=61 for both treatment groups; Geometric LS mean ± SE
Standard meals administered at t = 0 min; Geometric Mean Baseline Insulinogenic Index²: 0.4
Exenatide Reduced Postprandial Glucagon Levels to a Greater Extent Than Sitagliptin

Baseline | Exenatide | Sitagliptin
---|---|---
Plasma Glucagon (pg/mL) | | |
Time (min) | | |
-30 | 70 | 100 | 90
0 | 80 | 110 | 100
30 | 70 | 120 | 90
60 | 80 | 110 | 80
90 | 70 | 120 | 70
120 | 80 | 110 | 70
150 | 90 | 100 | 70
180 | 80 | 90 | 70
210 | 70 | 80 | 70
240 | 60 | 70 | 60

Patients with T2D; Evaluable population, n = 61 for all treatment groups; Mean ± SE
Exenatide Slowed Gastric Emptying Compared to Sitagliptin

*Acetaminophen is absorbed only after gastric emptying. Therefore, plasma levels of acetaminophen can be used to measure the gastric emptying rate.

Patients with T2D; Evaluable population, n=61 for all treatment groups; Mean ± SD; Acetaminophen was administered immediately before the standard meal
Exenatide Reduced Mean Caloric Intake

Mean Baseline Caloric Intake: 1071 kcal

- Changes in median caloric intake showed similar trends (exenatide, -138 kcal; sitagliptin, 63 kcal)

Patients with T2D; Evaluable ad lib cohort, n=25 for both treatment groups; LS mean ± SE; Standard meals administered at t=0 min
Both exenatide and sitagliptin were generally well tolerated
Mild-to-moderate nausea and vomiting were the most frequently reported events
- Nausea: exenatide, 34%; sitagliptin, 12%
- Vomiting: exenatide, 24%; sitagliptin, 3%
Study withdrawals due to adverse events (AEs)
- 2 patients on exenatide (nausea and symptomatic hypoglycaemia)
- 1 patient on sitagliptin (dizziness)
No major hypoglycaemic events were reported

Patients with T2D; ITT population N=95; AE indicates adverse event
Exenatide vs Sitagliptin MOA Study: Summary

- 2-hour PPG concentration was significantly reduced with exenatide compared with sitagliptin
- Compared with sitagliptin treatment, exenatide treatment led to
  - Greater reductions in
    - PPG concentrations over time
    - Postprandial glucose excursions
    - Postprandial glucagon levels
  - Improved insulinogenic index
  - Delayed gastric emptying
  - Decreased caloric intake
- Changes in FPG concentrations were comparable with exenatide and sitagliptin
- Both exenatide and sitagliptin were generally well tolerated

Clinical Trials of Exenatide
<table>
<thead>
<tr>
<th>Diet and Exercise</th>
<th>Oral Therapy</th>
<th>Multiple Oral Therapies</th>
<th>Insulin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide + MET¹ (N=336)</td>
<td>Exenatide + MET + SFU³ (N=733)</td>
<td>Exenatide + MET + SFU³ vs Insulin glargine + MET + SFU⁶ (N=551)</td>
<td></td>
</tr>
<tr>
<td>Exenatide + SFU² (N=377)</td>
<td>Exenatide ± MET + TZD⁴ (N=233)</td>
<td>Exenatide + MET or SFU vs Insulin glargine + MET or SFU⁶ (N=138)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exenatide + MET + SFU vs Biphasic insulin aspart + MET + SFU⁷ (N=501)</td>
<td></td>
</tr>
</tbody>
</table>

Phase 3 clinical studies

Large Phase 3 Clinical Studies: Study Design

- Randomised, double-blind, placebo-controlled, multicentre studies in patients with T2D
- No washout period
  - Exenatide or placebo administered subcutaneously before breakfast and evening meal

<table>
<thead>
<tr>
<th>Screening</th>
<th>Placebo 0.02 mL BID</th>
<th>Lead-in 0.02 mL BID</th>
<th>Exenatide 5 µg (0.02 mL) BID</th>
<th>Exenatide 10 µg (0.04 mL) BID</th>
<th>Placebo 0.02 mL or 0.04 mL BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>-4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
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<td></td>
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<tr>
<td>12</td>
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<td></td>
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<tr>
<td>24</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Time (week)

Large Phase 3 Clinical Studies: Exenatide Lowered HbA1c at 30 Weeks

ITT population; Mean (SE); MET (N=336), SFU (N=377), MET + SFU (N=733); *p<.005 versus placebo; **p<.001 versus placebo.
Mean baseline HbA1c ranged from 8.2% to 8.7% across all trial arms.
Large Phase 3 Clinical Studies: Exenatide Reduced PPG Over 30 Weeks

Mean (SE); N=138; Evaluable meal tolerance cohort.
p<.0001 for change in PPG from baseline to week 30, exenatide versus placebo group.
Data on file, Amylin Pharmaceuticals, Inc.
# Large Phase 3 Clinical Studies (Combined): Common Adverse Events

## Combined Results of 30-week Exenatide Phase 3 Studies

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=483)</th>
<th>Exenatide 5 µg (N=480)</th>
<th>Exenatide 10 µg (N=483)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>18%</td>
<td>39%</td>
<td>48%</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>8%</td>
<td>15%</td>
<td>25%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6%</td>
<td>11%</td>
<td>15%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4%</td>
<td>13%</td>
<td>13%</td>
</tr>
<tr>
<td>Headache</td>
<td>6%</td>
<td>10%</td>
<td>7%</td>
</tr>
<tr>
<td>Feeling jittery</td>
<td>4%</td>
<td>9%</td>
<td>10%</td>
</tr>
</tbody>
</table>

*Exenatide did not increase the incidence of hypoglycaemia when combined with MET*
Large Phase 3 Clinical Studies (Combined): Nausea Decreased Over Time

ITT 30-week data; N=1446.
Data on file, Amylin Pharmaceuticals, Inc.
Pancreatitis Is a Rare Adverse Event

♦ Exenatide
  • Spontaneous cases of pancreatitis have been reported with use of exenatide
  • As of January 31, 2009 the cumulative reporting rate of pancreatitis is 0.57 events per 1000 patient years of exenatide exposure

♦ General population*
  • Recent estimates of the incidence of pancreatitis in the general US population are as follows:
    • 0.7 events per 1000 adults per year
    • Severe disease develops in 15-20% of those pancreatitis cases
    • Death occurs in 2-9% of cases
    • Drug-induced pancreatitis is a relatively rare event (1.4-2.0% of all cases)

♦ Patients with T2D
  • A recent epidemiological study has reported that patients with T2D are at nearly 3 times the risk of developing pancreatitis than those without diabetes

*Note: The pancreatitis rates in the general population should not be directly compared to those rates seen in exenatide-treated patients.

Pancreatitis – Epidemiological Studies

Retrospective cohort study (large US health care claims database)
- risk of pancreatitis in T2D vs ND cohort (RR, 95% CI: 2.83;2.61-3.06)\(^5\)

Retrospective cohort study (United Health Care)
- no increased risk of medical chart confirmed acute pancreatitis (RR and 95% CI: 0.5; 0.2 – 0.9).
- Suggested no increase risk of among recent and past exenatide user cohorts.\(^1\)

Retrospective cohort study (IMS Life-Link database)
- no increased risk of pancreatitis associated with current (OR, 95% CI: 0.9; 0.6 - 1.4), recent (1.0; 0.5 - 1.8), or past (0.6; 0.4 – 1.0) use of exenatide.\(^2\)

Active safety signal detection (i3 Aperio active drug safety surveillance program)
- found risk of pancreatitis was comparable for initiators of exenatide (RR, 95% CI: 1.0; 0.6 – 1.7) vs. metformin or glyburide initiators.\(^3\)

Retrospective cohort study (large medical & pharmacy claims)
- risk of acute pancreatitis was similar in the exenatide vs. diabetic control group (adjusted HR, 95% CI: 0.9 ;0.6-1.5).\(^4\)

Long-term Follow-up of Exenatide-treated Patients in Uncontrolled Extension Studies

Baseline 8.2 ±0.1%
Week 156
-1.0% (95% CI: -1.1 to -0.8%; p<.0001)

Baseline 99.3 ± 1.2 kg
Week 156
-5.3 kg (95% CI: -6.0 to -4.5 kg; p<.0001)

N=217; Mean; CI = confidence interval
Open-label Extension: 68% of 3-year Completers Lost Weight and Had Reduced HbA1c

N=217
Baseline HbA1c ≥9% Improved With Exenatide

Open-label Extension

Baseline HbA1c (%)
- Baseline HbA1c ≥9% (n=59) 9.7
- Baseline HbA1c <9% (n=182) 7.8

Change in HbA1c (%)

Week 30
- Baseline HbA1c ≥9% -0.9%
- Baseline HbA1c <9% -2.0%

Week 130
- Baseline HbA1c ≥9% -0.7%
- Baseline HbA1c <9% -2.1%

2.5-year completers; n=241 at weeks 30 and 130; mean ± SE
Data on file, Amylin Pharmaceuticals, Inc.
Improvement in Cardiovascular Risk Factors With 3.5 Years of Exenatide Treatment

Placebo-controlled/Open-label Extension (Combined)

Mean Change (%)

TG  LDL  TC  HDL  SBP  DBP

-12%  -6%  -5%  +24%  -2%  -4%

N=151;  *p<.001  **p<.05

TG = triglycerides; SBP = systolic BP; DBP = diastolic BP
Elevated ALT and AST are often associated with NASH or fatty liver disease.

Mean ± SE; ALT = alanine aminotransferase; AST = aspartate aminotransferase; NASH = nonalcoholic steatohepatitis.

Elevated ALT is often associated with NASH or fatty liver disease.

N=116
Exenatide in the T2D Treatment Continuum

Diet and Exercise

- Exenatide + MET\(^1\) (N=336)
- Exenatide + SFU\(^2\) (N=377)

Oral Therapy

- Exenatide + MET\(^3\) + SFU\(^3\) (N=733)
- Exenatide ± MET + TZD\(^4\) (N=233)

Multiple Oral Therapies

- Exenatide + MET + SFU vs Insulin glargine + MET + SFU\(^5\) (N=551)
- Exenatide + MET or SFU vs Insulin glargine + MET or SFU\(^6\) (N=138)
- Exenatide + MET + SFU vs Biphasic insulin aspart + MET + SFU\(^7\) (N=501)

Insulin Therapy

Exenatide vs Insulin: Changes in HbA1c and Weight in 3 Head-to-Head Studies

Comparable glycaemic control for exenatide and insulin
Weight loss for exenatide vs weight gain for insulin

*This study was a crossover design. Therefore, only the weight data from the initial phase was used to avoid confounding the data
## Exenatide vs Insulin: Most Common Adverse Events in 3 Head-to-Head Studies

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Exenatide (N=673)</th>
<th>Insulin (N=517)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>45%</td>
<td>5%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15%</td>
<td>4%</td>
</tr>
<tr>
<td>Headache</td>
<td>6%</td>
<td>7%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>8%</td>
<td>10%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8%</td>
<td>3%</td>
</tr>
<tr>
<td>Influenza</td>
<td>5%</td>
<td>9%</td>
</tr>
</tbody>
</table>

Relationship of Baseline HbA1c to Change in HbA1c at Endpoint

- Exenatide: Change in HbA1c = 3.7 - 0.5*Baseline
- Insulin Aspart 30/70: Change in HbA1c = 2.9 - 0.4*Baseline

ITT sample; regression of change in HbA1c versus baseline HbA1c shown
Data on file, Lilly USA, LLC.
Exenatide/Biphasic Insulin Aspart Comparator Trial: Change in Body Weight

Exenatide Premixed Insulin

Using Exenatide
Exenatide BID on the Markets in the US and Europe

♦ 60 doses per pen (30-day supply)
♦ After first use, exenatide can be kept at a room temperature not to exceed 77°F (25°C)

♦ Take exenatide within 1 hour before a meal
♦ No dosage adjustments based on meal size or exercise
♦ No additional glucose monitoring required
ADA/EASD Consensus Statement for T2D

Tier 1: well-validated core therapies

Diagnosis:
- Lifestyle + Metformin

Step 1
- Lifestyle + Metformin + Basal insulin
- Lifestyle + Metformin + Sulfonylurea

Step 2
- Lifestyle + Metformin + Intensive insulin

Step 3

Tier 2: less well-validated core therapies

- Lifestyle + Metformin + Pioglitazone (no hypoglycaemia/edema (CHF)/bone loss)
- Lifestyle + Metformin + GLP-1 agonist (no hypoglycemia/weight loss/nausea/vomiting)

Lifestyle + Metformin + Basal insulin

CHF = congestive heart failure
Exenatide is a first-in-class GLP-1 receptor agonist that shares several glucoregulatory actions with GLP-1:
- Enhances glucose-dependent insulin secretion
- Reduces postprandial glucagon levels
- Slows gastric emptying rate
- Reduces food intake and body weight
- β-cell effects

Well-established safety and efficacy profile across the T2D treatment continuum

When initiating treatment with exenatide
- No dosage adjustments based on meal size or exercise
- No additional glucose monitoring required

Based on the ADA/EASD consensus statement, in selected clinical settings, exenatide is a reasonable therapeutic option

Exenatide once weekly dosing
- Currently being investigated
- Fewer injections
- Potential benefits as a result of increased half-life (pharmacokinetics)
Back-up Slides
Large Phase 3 Clinical Studies (Combined): Anti-exenatide Antibodies

• 38% of patients had low-titre anti-exenatide antibodies at 30 weeks
  • For this group, the HbA1c was generally comparable to that observed in those without antibody titres

• An additional 6% of patients had higher titre antibodies at 30 weeks

• In 3% of the total patients given exenatide in the controlled studies, the glycaemic response to exenatide appeared diminished

BYETTA® European Package Insert, 2006.
LEAD-6: HbA$_{1c}$ change over 26 weeks - All subjects

Estimated treatment difference for changes from baseline
Least square mean: –0.33
95% CI [– 0.47; – 0.18]
*** $p<0.0001$

Mean (2SE)

- Liraglutide 1.8 mg OD
- Exenatide 10 µg BID
Large Phase 3 Clinical Studies: Exenatide Reduced FPG at 30 Weeks

ITT population; Mean (SE); MET (N=336), SFU (N=377), MET + SFU (N=733); *p<.05 versus placebo.
Mean baseline FPG ranged from 9.3 mmol/L to 10.8 mmol/L across all trial arms.
Large Phase 3 Clinical Studies: Exenatide Reduced Body Weight Over 30 Weeks

ITT population; Mean (SE); MET (N=336), SFU (N=377), MET + SFU (N=733); *p<.05 versus placebo; **p<.001 versus placebo.

Mean baseline weight ranged from 95 kg to 101 kg across all trial arms.

**Large Phase 3 Clinical Studies (Combined): Exenatide Reduced HbA1c and Weight**

---

**Change in HbA1c (%)**

- **Placebo BID**: +0.1
- **Exenatide 5 µg BID**: -0.6 (p<0.005)
- **Exenatide 10 µg BID**: -0.9 (p<0.005)

**Change in Weight (kg)**

- **Placebo BID**: -0.7
- **Exenatide 5 µg BID**: -1.4 (p<0.005)
- **Exenatide 10 µg BID**: -1.9 (p<0.005)

---

ITT 30-week data; N=1446; Mean (SE); *p<.005; Weight was a secondary endpoint. Data on file, Amylin Pharmaceuticals, Inc.
**Exenatide Has Been Studied Across all Stages of the T2D Treatment Continuum**

- **Diet and Exercise**
- **Oral Therapy**
  - **Exenatide + MET**
  - **Exenatide + SFU**
  - **Exenatide + MET vs. Sitagliptin + MET: MOA study**
  - **Exenatide + MET + SFU**
  - **Exenatide ± MET + TZD**
  - **Exenatide vs Insulin**

Exenatide also has a proven history with 3.5 years on the market, 7.5 million prescriptions written,¹ and 6 years of patient experience.

*This study was not a controlled head-to-head study*

¹ IMS Health data, October 2008.
Large Phase 3 Clinical Studies (Combined): Open-Label Extension

- Treatment was open-label and uncontrolled
  - Extension study of subjects from original placebo-controlled trials
  - Subjects with T2D who were unable to achieve glycaemic control with MET and/or SFU

Open-Label Extension: Patient Disposition

3-year Eligible ITT Population: 527

3-year Completers: 217

Withdrew: 310

<table>
<thead>
<tr>
<th>Reason</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Event</td>
<td>58</td>
<td>(11%)</td>
</tr>
<tr>
<td>Loss of Glucose Control</td>
<td>18</td>
<td>(3%)</td>
</tr>
<tr>
<td>Patient/Investigator Decision</td>
<td>217</td>
<td>(41%)</td>
</tr>
<tr>
<td>Protocol Violation</td>
<td>17</td>
<td>(3%)</td>
</tr>
</tbody>
</table>

# Open-label Extension: Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>3-year Completers (n=217)</th>
<th>3.5-year Completers (n=151)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex (%)</strong>: male/female</td>
<td>64/36</td>
<td>68/32</td>
</tr>
<tr>
<td><strong>Age (y)</strong></td>
<td>58 ± 10</td>
<td>57 ± 9</td>
</tr>
<tr>
<td><strong>Race (%)</strong>: Caucasian/Black/Hispanic/Other</td>
<td>83/10/6/1</td>
<td>84/9/7/1</td>
</tr>
<tr>
<td><strong>Duration of diabetes (y)</strong></td>
<td>8 ± 6</td>
<td>8 ± 6</td>
</tr>
<tr>
<td><strong>Baseline HbA1c (%)</strong></td>
<td>8.2 ± 1.0</td>
<td>8.2 ± 1.0</td>
</tr>
<tr>
<td><strong>Baseline body weight (kg)</strong></td>
<td>99 ± 18</td>
<td>100 ± 19</td>
</tr>
<tr>
<td><strong>Baseline BMI (kg/m²)</strong></td>
<td>33.5 ± 5.3</td>
<td>33.4 ± 5.4</td>
</tr>
<tr>
<td><strong>Fasting plasma glucose (mmol/L)</strong></td>
<td>9.6 ± 2.5</td>
<td>9.4 ± 2.5</td>
</tr>
</tbody>
</table>

*Mean ± SD.*

Open-label Extension: 84% of 3-year Completers Experienced Weight Reduction

84% (182/217) of patients had weight loss

16% (35/217) of patients had no weight change or had weight gain

N=217
Open-label Extension: HbA1c Change by 3-Year Weight-change Quartiles

N=217. Mean + SEM
Open-label Extension: No Age-related Difference in Patient Response to Exenatide

* p<0.0001 change from baseline; Mean ± SEM
## Improvement in Cardiovascular Risk Factors With 3.5 Years of Exenatide Treatment (N=151)

<table>
<thead>
<tr>
<th>Cardiovascular Risk Factor</th>
<th>Baseline (Mean ± SEM)</th>
<th>Change from Baseline (Mean ± SEM)</th>
<th>Mean Change</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>2.5 ± 0.1</td>
<td>-0.5 ± 0.1</td>
<td>-12%</td>
<td>-0.8 to -0.2</td>
<td>.0003</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>4.8 ± 0.1</td>
<td>-0.3 ± 0.1</td>
<td>-5%</td>
<td>-0.4 to -0.1</td>
<td>.0007</td>
</tr>
<tr>
<td>HDL–C (mmol/L)</td>
<td>1.0 ± 0.0</td>
<td>0.2 ± 0.0</td>
<td>+24%</td>
<td>0.2 to 0.3</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>LDL–C (mmol/L)</td>
<td>2.9 ± 0.1</td>
<td>-0.3 ± 0.1</td>
<td>-6%</td>
<td>-0.5 to -0.2</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>129.3 ± 1.0</td>
<td>-3.5 ± 1.2</td>
<td>-2%</td>
<td>-5.9 to -1.0</td>
<td>.0063</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>79.2 ± 0.6</td>
<td>-3.3 ± 0.8</td>
<td>-4%</td>
<td>-4.9 to -1.7</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Exenatide/Insulin Glargine Comparator Trial: Study Design

- 26-week treatment, BID fixed-dose exenatide versus QD insulin glargine titration
- Primary endpoint: Change in HbA1c
- ITT sample: N=549 randomised patients with ≥1 postbaseline measurement

Screening (HbA1c ≥7.0% to ≤10.0%)

Randomisation

Current MET/SFU Therapy

Exenatide 5 µg + MET/SFU

Exenatide 10 µg + MET/SFU

Insulin Glargine + MET/SFU
(insulin titrated to target FPG <5.6 mmol/L by daily monitoring)

Time (week)

-4 -2 0 2 4 8 12 18 26

# Exenatide/Insulin Glargine Comparator Trial: Patient Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Exenatide</th>
<th>Insulin Glargine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male (%)</td>
<td>55.0%</td>
<td>56.6%</td>
</tr>
<tr>
<td>Age (y)</td>
<td>59.8 ± 8.8</td>
<td>58.0 ± 9.5</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>87.5 ± 16.9</td>
<td>88.3 ± 17.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.4 ± 4.4</td>
<td>31.3 ± 4.6</td>
</tr>
<tr>
<td>FSG (mmol/L)</td>
<td>10.1 ± 2.6</td>
<td>10.4 ± 2.9</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.2 ± 1.0</td>
<td>8.3 ± 1.0</td>
</tr>
<tr>
<td>Duration of diabetes (y)</td>
<td>9.9 ± 6.0</td>
<td>9.2 ± 5.7</td>
</tr>
</tbody>
</table>

Mean ± SD shown.
Exenatide/Insulin Glargine Comparator Trial: Achieved Equivalent Reductions in HbA1c

ITT population: Mean ± SE shown.
Exenatide/Insulin Glargine Comparator Trial: Exenatide Reduced PPG Excursions

Exenatide/Insulin Glargine Comparator Trial: Exenatide Resulted in Progressive Weight Reductions

Exenatide/Insulin Glargine Comparator Trial: Safety and Tolerability

- Exenatide and insulin glargine had low overall rates of hypoglycaemia (7.3 versus 6.3 events/patient-year)
  - Nocturnal hypoglycaemia was lower for exenatide
  - Daytime hypoglycaemia was lower for insulin glargine
  - Four episodes of severe hypoglycaemia occurred in each arm
    - None required medical assistance
  - No study withdrawals due to hypoglycaemia

- Most common adverse events for exenatide were GI-related
  - Nausea (exenatide 57%, insulin glargine 9%)
    - Mostly mild-to-moderate episodes, occurring early in treatment
  - Vomiting (exenatide 17%, insulin glargine 4%)
    - Decreasing incidence throughout the study

Exenatide/Insulin Glargine Crossover Noninferiority Trial: Study Design

 Patients: MET or SFU HbA1c ≥7.1% and ≤11.0%

Week of Treatment ± 1

-2 0 16 32

Randomisation Screenning

Treatment Period I

Exenatide 10 µg (BID) †

SFU or MET

Insulin Glargine (QD) ‡

Crossover

Treatment Period II

Exenatide 10 µg (BID) †

SFU or MET

Insulin Glargine (QD) ‡

†Patients were treated with 5 µg exenatide BID for the first 4 weeks and then 10 µg exenatide BID thereafter; ‡Insulin glargine was titrated targeting a fasting glucose ≤5.6 mmol/L. Mean endpoint insulin glargine dose: Treatment Period 1, 28.6 ± 16.8 IU/day (n=69); Treatment Period 2, 25.7 ± 17.6 IU/day (n=57). Barnett AH, et al. Clin Ther. 2007;29:2333-2348.
## Exenatide/Insulin Glargine Crossover Noninferiority Trial: Patient Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Exenatide/ Insulin Glargine (n=68)</th>
<th>Insulin Glargine/ Exenatide (n=70)</th>
<th>Total (N=138)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>8.89 ± 0.13</td>
<td>9.00 ± 0.13</td>
<td>8.95 ± 0.09</td>
</tr>
<tr>
<td>FSG (mmol/L)</td>
<td>11.8 ± 0.4</td>
<td>12.2 ± 0.4</td>
<td>12.0 ± 0.3</td>
</tr>
<tr>
<td>Duration of diabetes (y)</td>
<td>6.6 ± 0.6</td>
<td>8.3 ± 0.7</td>
<td>7.4 ± 0.4</td>
</tr>
<tr>
<td>Age (y)</td>
<td>54.5 ± 1.1</td>
<td>55.3 ± 1.2</td>
<td>54.9 ± 0.8</td>
</tr>
<tr>
<td>Gender, male (%)</td>
<td>48.5</td>
<td>45.7</td>
<td>47.1</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>85.6 ± 2.0</td>
<td>84.0 ± 2.0</td>
<td>84.8 ± 1.4</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.3 ± 0.5</td>
<td>30.9 ± 0.5</td>
<td>31.1 ± 0.4</td>
</tr>
<tr>
<td>Oral antidiabetic agent, (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MET</td>
<td>55.9</td>
<td>54.3</td>
<td>55.1</td>
</tr>
<tr>
<td>SFU</td>
<td>44.1</td>
<td>45.7</td>
<td>44.9</td>
</tr>
</tbody>
</table>

ITT sample, N=138; mean ± SEM or percentage.
Exenatide/Insulin Glargine Crossover Noninferiority Trial: Change in HbA1c at Endpoint in MET- and SFU-treated Patients

-1.8 -1.6 -1.4 -1.2 -1.0 -0.8 -0.6 -0.4 -0.2 0

MET SFU

Change in HbA1c (%)

Exenatide (n=136) Insulin Glargine (n=127)

Exenatide/Insulin Glargine Crossover Noninferiority Trial: Percent of Patients to HbA1c Targets at Endpoint

ITT sample, N=138
Exenatide/Insulin Glargine Crossover Noninferiority Trial: 2-hour Postprandial Glucose Excursions

Intent-to-treat sample, N=138; LS mean ± SEM; *p<.001, exenatide versus insulin glargine; **p=.016, exenatide versus insulin glargine.
Exenatide/Insulin Glargine Crossover Noninferiority Trial: Time Course of Body Weight by Treatment

![Graph showing the time course of body weight change by treatment. The graph compares Exenatide and Insulin Glargine.]

- **Exenatide**
  - Time (week): 0, 2, 4, 6, 8, 12, 16, 18, 20, 22, 24, 28, 32
  - Change in Body Weight (kg): –3, –2, –1, 0, 1, 2
  - n=70

- **Insulin Glargine**
  - Time (week): 0, 2, 4, 6, 8, 12, 16, 18, 20, 22, 24, 28, 32
  - Change in Body Weight (kg): –3, –2, –1, 0, 1, 2
  - n=68

Legend:
- Exenatide (yellow line)
- Insulin Glargine (green line)
### Exenatide/Insulin Glargine Crossover Noninferiority Trial: Adverse Events Occurring in ≥5% of Study-Drug-Treated Patients†

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Insulin Glargine N=127</th>
<th>Exenatide N=136</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (3.1)</td>
<td>58 (42.6)</td>
</tr>
<tr>
<td>Headache</td>
<td>12 (9.4)</td>
<td>17 (12.5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (3.1)</td>
<td>13 (9.6)</td>
</tr>
<tr>
<td>Cough</td>
<td>11 (8.7)</td>
<td>6 (4.4)‡</td>
</tr>
<tr>
<td>Influenza</td>
<td>15 (11.8)</td>
<td>11 (8.1)‡</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>10 (7.9)</td>
<td>4 (2.9)‡</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7 (5.5)‡</td>
<td>9 (6.6)‡</td>
</tr>
</tbody>
</table>

Exenatide/Insulin Glargine Crossover Noninferiority Trial: Hypoglycaemia Incidence

ITT sample, N=138; LS mean (SEM); *p=0.010
Exenatide/Insulin Glargine Crossover Noninferiority Trial: Overall Hypoglycaemia Rate

ITT sample, N=138; Incidence densities (number of episodes/exposure) ± 95% CI.
*p=.039, exenatide versus insulin glargine; **p<.001, exenatide + MET versus insulin glargine + MET.
Exenatide/Insulin Glargine Crossover Noninferiority Trial: Nocturnal Hypoglycaemia Rate

ITT sample, N=138; Incidence densities (number of episodes/exposure) ± 95% CI .
*p<.001, exenatide versus insulin glargine; **p=.002, exenatide + MET versus insulin glargine + MET.
Exenatide/Biphasic Insulin Aspart Comparator Trial: Study Design

♦ Primary Hypothesis: Glycaemic control achieved with exenatide is noninferior to that of premixed insulin in patients failing to reach treatment goals with MET plus SFU

♦ Noninferiority will be demonstrated by excluding the 0.4% noninferiority margin with the upper limit of a two-sided 95% CI for the mean difference between treatments

Screening (HbA1c ≥7.0% to ≤11.0%; BMI ≥25 and ≤40 kg/m²)

Premixed insulin in this study refers to biphasic insulin aspart (30% rapid-acting insulin aspart);
Mean dose of premixed insulin increased from 15.7 U/d (week 2) to 24.4 U/d (week 52).
### Exenatide/Biphasic Insulin Aspart Comparator Trial: Patient Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Exenatide</th>
<th>Premixed Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>59 (9)</td>
<td>58 (9)</td>
</tr>
<tr>
<td>Gender, male %</td>
<td>53</td>
<td>49</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>85.5 (15.7)</td>
<td>83.4 (15.6)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>30.6 (4.0)</td>
<td>30.2 (4.2)</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>11.0 (2.7)</td>
<td>11.3 (2.8)</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>8.6 (1.0)</td>
<td>8.6 (1.1)</td>
</tr>
<tr>
<td>Duration of diabetes, y</td>
<td>9.8 (6.3)</td>
<td>10.0 (6.2)</td>
</tr>
</tbody>
</table>

ITT sample, mean (SD) shown.
**Exenatide/Biphasic Insulin Aspart Comparator Trial: Changes in HbA1c at Endpoint**

- **Patients to Target (%)**
  - Exenatide: 32%
  - Premixed Insulin: 24%

- **Change in HbA1c (%)**
  - Exenatide: -1.04%
  - Premixed Insulin: -0.89%

- **95% CI**: -0.32 to 0.01, p=.067

*ITT sample; left panel; ITT sample, mean change ± SE shown; Right panel: between-group difference *p=.038 Nauck MA, et al. Diabetologia. 2007;50:259-267.*
Exenatide/Biphasic Insulin Aspart Comparator Trial: 7-Point SMBG Profiles

ITT sample, mean (SE) shown; significantly lower mean glucose level observed for exenatide *p<.001, premixed insulin **p=.0370; †p=.0040; ‡p=.002.
The most common adverse event with exenatide was nausea
  • Exenatide: 33%, premixed insulin: 0.4%
  • Mild to moderate, most common at study initiation
  • Low dropout rate, 3.5%

Exenatide and premixed insulin had low overall rates of hypoglycaemia (events/patient-year)
  • Daytime: Exenatide 4.1; premixed insulin 4.4
  • Nocturnal: Exenatide 0.6; premixed insulin 1.1
  • No severe hypoglycaemia was reported during the study

**Exenatide Reduced Fasting Hyperglycaemia in Patients With T2D**

Mean (SE); N=12; p<.0001 for glucose; p<.001 for insulin.

Exenatide Reduced Postprandial Hyperglycaemia in Patients With T2D

Mean (SE); N=109; p≤.004.
Exenatide Reduced β-Cell Workload in T2D

N=20; Mean (SE).
Exenatide Dose-Dependently Slowed Gastric Emptying

LS Geometric Means shown.
*p<.01 versus placebo.
Exenatide Improved β-Cell Sensitivity in Patients With T2D

Mean (SE); N=9; p<.002.
Exenatide in Patients Using TZDs With or Without MET

♦ To compare the effects of exenatide versus placebo on glycaemic control in patients with T2D suboptimally controlled on a TZD or a TZD plus MET
♦ Primary endpoint
  • Change from baseline for HbA1c
♦ Secondary endpoints
  • FSG
  • Seven-point SMBG test
  • Body weight
  • Percent of patients achieving HbA1c ≤7.0% and <6.5%

## Exenatide in Combination With TZDs: Patient Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Exenatide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male (%)</td>
<td>53.7%</td>
<td>57.1%</td>
</tr>
<tr>
<td>Age (y)</td>
<td>55.6 ± 10.8</td>
<td>56.6 ± 10.2</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>97.5 ± 18.8</td>
<td>96.9 ± 19.0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>34.0 ± 5.1</td>
<td>34.0 ± 5.0</td>
</tr>
<tr>
<td>FSG (mmol/L)</td>
<td>9.1 ± 2.6</td>
<td>8.8 ± 1.9</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.9 ± 0.9</td>
<td>7.9 ± 0.8</td>
</tr>
<tr>
<td>Duration of diabetes (y)</td>
<td>7.3 ± 4.9</td>
<td>8.2 ± 5.8</td>
</tr>
</tbody>
</table>

Mean ± SD, ITT patient sample.
Exenatide in Combination With TZDs: HbA1c at Baseline and Week 16

ITT patient sample, Mean ± SE, *-0.98 refers to change from baseline to week 16 [95% CI, -1.21% to -.74%], n=117 for exenatide, n=105 for placebo. Adapted from Zinman B, et al. Ann Intern Med. 2007;146:477-485.
Exenatide in Combination With TZDs: Patients Achieving Target HbA1c

Per-protocol patient sample: randomised patients who had no protocol violations and either completed the protocol or received at least 16 weeks of treatment. Baseline HbA1c >7% or 6.5%. *p<.001.

Duplicate Slides
mg/dL and lbs
Exenatide vs Sitagliptin MOA Study: Demographic and Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Evaluable Patients (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, Female/Male (%)</td>
<td>54/46</td>
</tr>
<tr>
<td>Age (y)</td>
<td>54 ± 9</td>
</tr>
<tr>
<td>Race, Caucasian/Black/Hispanic (%)</td>
<td>30/8/62</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>167.0 ± 9.9</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>91.5 ± 18.8</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32.6 ± 5.1</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>8.5 ± 1.2</td>
</tr>
<tr>
<td>Duration of diabetes (y)</td>
<td>7 ± 5</td>
</tr>
<tr>
<td>Fasting triglycerides (mg/dL)</td>
<td>166 ± 93</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>178 ± 48</td>
</tr>
<tr>
<td>2-hr PPG (mg/dL)</td>
<td>245 ± 65</td>
</tr>
</tbody>
</table>

Patients with T2D; MET background; Mean ± SD, unless otherwise indicated; BMI = body mass index; FPG = fasting plasma glucose. DeFronzo RA, et al. Curr Med Res Opin. 2008;24:2943-2952.
GLP-1 Effects Are Glucose Dependent in T2D

N=10; Mean ± standard error of the mean; *p<.05; †Plasma
Tests were performed after an overnight fast.
Exenatide Induced Islet Neogenesis in Partially Pancreatectomised Rats

Mean (SE).

Expansion of β-cell mass resulted from enhanced β-cell neogenesis following exendin-4 treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>β-Cell Mass (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham + Saline</td>
<td>0</td>
</tr>
<tr>
<td>Sham + exenatide</td>
<td>2</td>
</tr>
<tr>
<td>Pancreatectomy + Saline</td>
<td>4</td>
</tr>
<tr>
<td>Pancreatectomy + exenatide</td>
<td>6</td>
</tr>
</tbody>
</table>

p < 0.05

p < 0.01
Exenatide Reduced PPG Concentrations to a Greater Extent Than Sitagliptin

Patients with T2D; Evaluable population, n = 61 for all treatment groups; Mean ± SE; * least square (LS) mean ± SE, P<0.0001
Exenatide vs Insulin: Changes in HbA1c and Weight in 3 Head-to-Head Studies

*This study was a crossover design. Therefore, only the weight data from the initial phase was used to avoid confounding the data.


Comparable glycaemic control for exenatide and insulin
Weight loss for exenatide vs weight gain for insulin