# GLP-1-Based Therapy as a New Treatment

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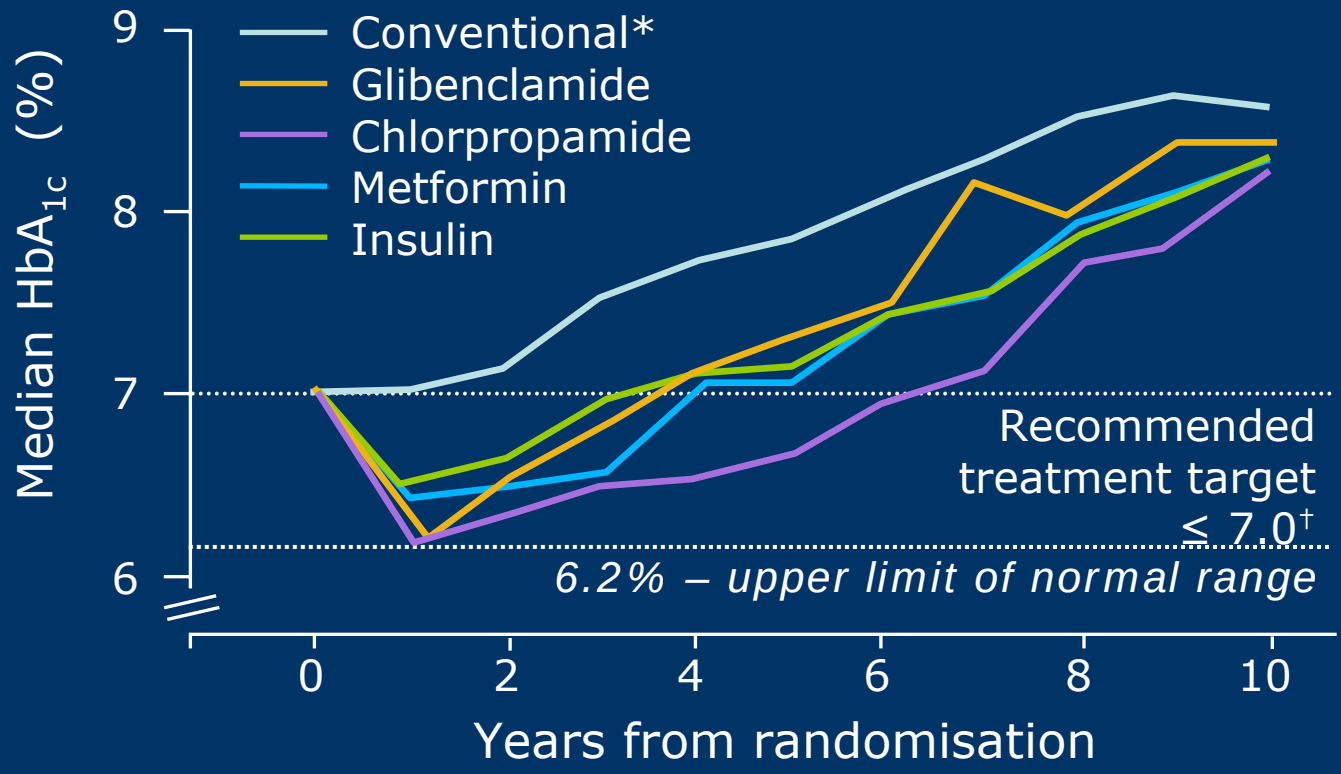
# Overview

1. Why do we need new treatments for diabesity?
2. What makes GLP-1 a good therapeutic target?
3. Harnessing the potential of GLP-1:
    - Incretin mimetics
    - Incretin enhancers
4. Conclusions

# Why do we need new treatments for diabesity?

# UKPDS Clearly Showed the Need for New Diabetes Treatments




The prevelance of overweight and obesity is increasing
This is contributing to the diabetes epidemic

Adapted from: UKPDS 34. Lancet 1998

# Why do We Need New Therapeutic Agents?

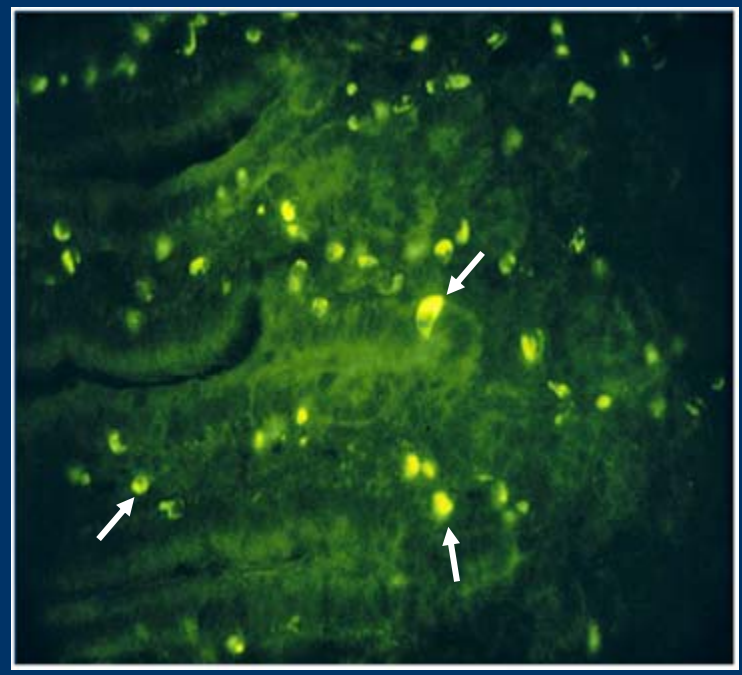
1. Metformin fails with time and has tolerability issues (GI side effects)
2. SUs have side effects (hypoglycaemia, weight gain) and may cause accelerated beta cell failure
3. TZDs may have severe side effects (heart failure, myocardial infarction, osteoporosis, fluid accumulation, weight gain, cancer)
4. Current combination therapies do not halt progression of disease
5. Insulin therapy will always be instituted too late because of side effects (hypoglycaemia, weight gain) and inconvenience

Many patients cannot maintain satisfactory glycaemic control with existing agents
Most are associated with weight gain

# What makes GLP-1 a good therapeutic target?

# What is GLP-1?

- A 30 amino acid peptide
- Secreted from endocrine cells in the small intestinal mucosa
- Released in response to meal ingestion
- Responsible for the incretin effect (together with GIP)



GLP-1 positive endocrine L-cells (green) in human small intestine

# GLP-1 has Multiple Effects

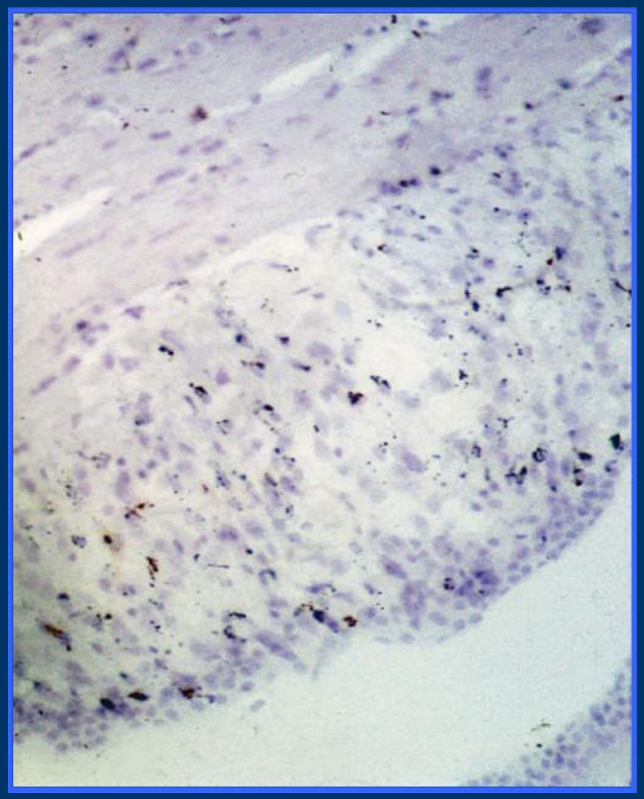
1. Efficacious glucose lowering
   - ↑ insulin secretion (glucose-dependent)
   - Upregulates insulin gene expression & all steps in insulin biosynthesis
   - Upregulates expression of genes essential for β-cell function (Glut 2, glucokinase etc)
   - ↑ β-cell mass (animal models) - ↑ neogenesis & proliferation, ↓ apoptosis
   - ↓ glucagon secretion (glucose-dependent) → ↓ hepatic glucose output
   - Delayed gastric emptying
2. Body weight lowering
   - Delayed gastric emptying
   - ↑ fullness and satiety, ↓ appetite → ↓ food intake
3. Disease modifying potential
   - ↑ β-cell glucose sensitivity
   - Improved β-cell function
   - ↑ β-cell mass (animal models) - ↑ neogenesis & proliferation, ↓ apoptosis
   - Beneficial cardiovascular effects

# GLP-1:
# Therapeutic Potential in Diabesity

| Type 2 diabetic phenotype | Actions of GLP-1 |
|---|---|
| • Impaired β-cell function | •↑ insulin secretion and biosynthesis<br>• Improves β-cell function (glucose sensitivity, proinsulin/insulin ratio)<br>• Upregulates other genes essential for β-cell function (eg. GLUT 2, glucokinase) |
| • Reduced β-cell mass | •↑ β-cell proliferation/differentiation<br>•↓ β-cell apoptosis<br>〉 animal studies + in vitro |
| • Glucagon hypersecretion | •↓ glucagon secretion |
| • Overeating, obesity | •↓ gastric emptying, ↑ satiety, ↓ appetite<br>→ ↓ food intake & weight loss |
| • Macrovascular complications | • Beneficial cardiovascular effects |
| • Insulin resistance | *Actions which may be secondary to improved metabolic control*<br>• Improvements in insulin sensitivity |

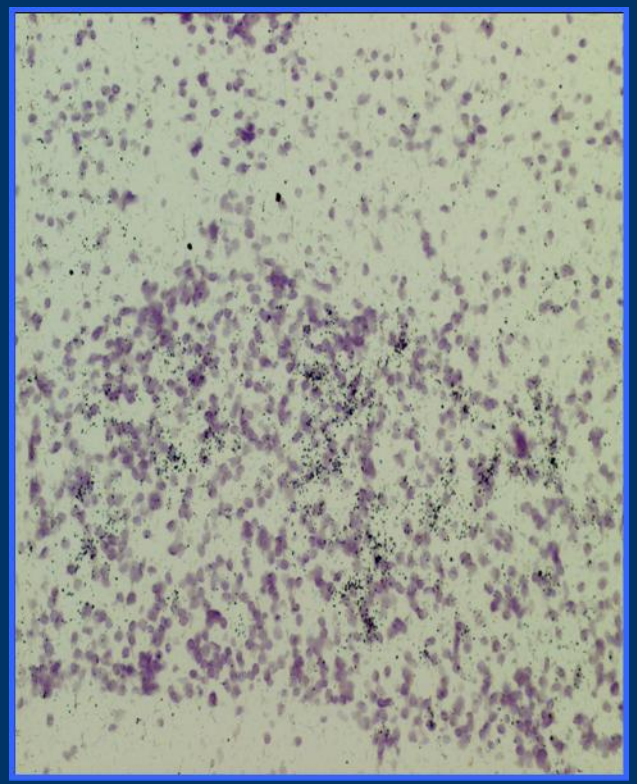
# Peripheral GLP-1 Accesses Areas of the Brain Associated with Food Intake, and these contain GLP-1 Receptors

Access of peripherally injected $^{125}$I-GLP-1 to area postrema



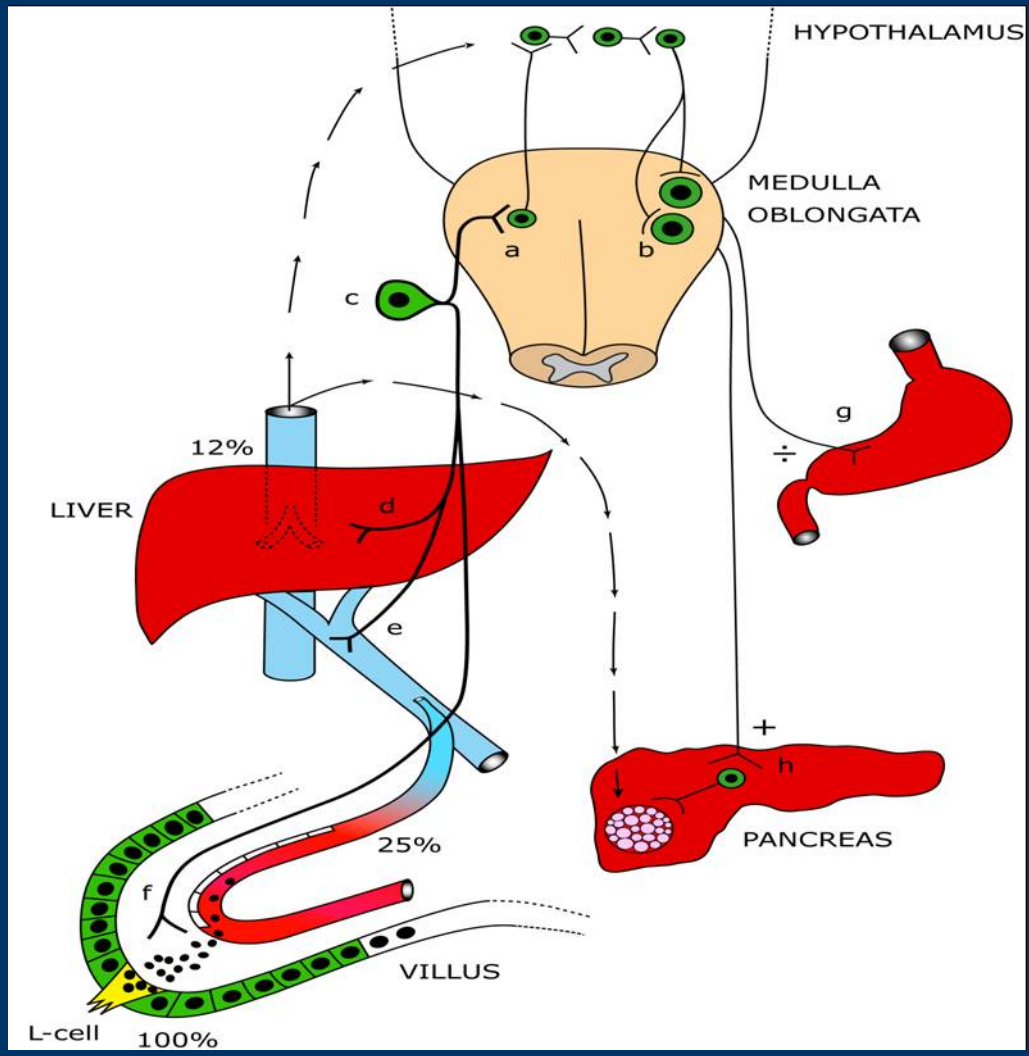
Ørskov et al, Diabetes,1996

GLP-1 receptor in situ hybridisation in the area postrema



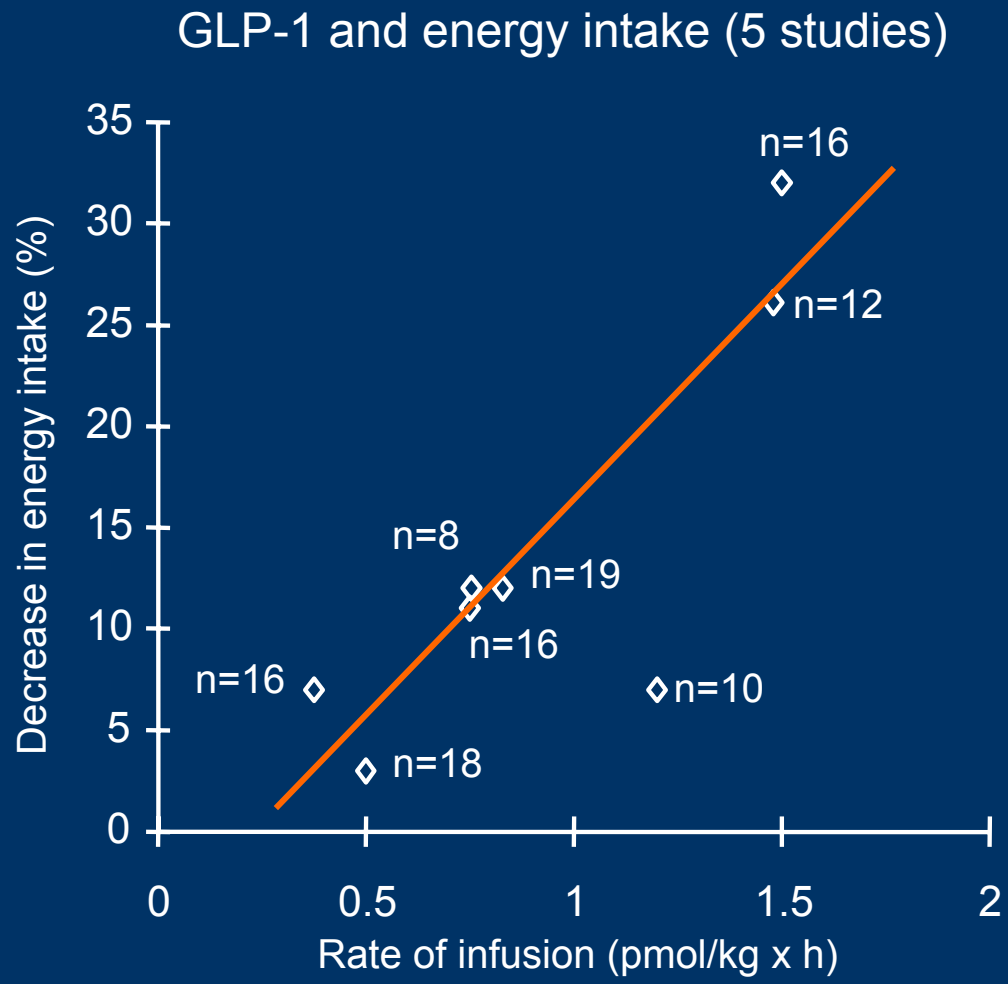
Philip Larsen , Rheoscience, Copenhagen

# GLP-1 may Influence Food Intake by Neural and Endocrine Mechanisms



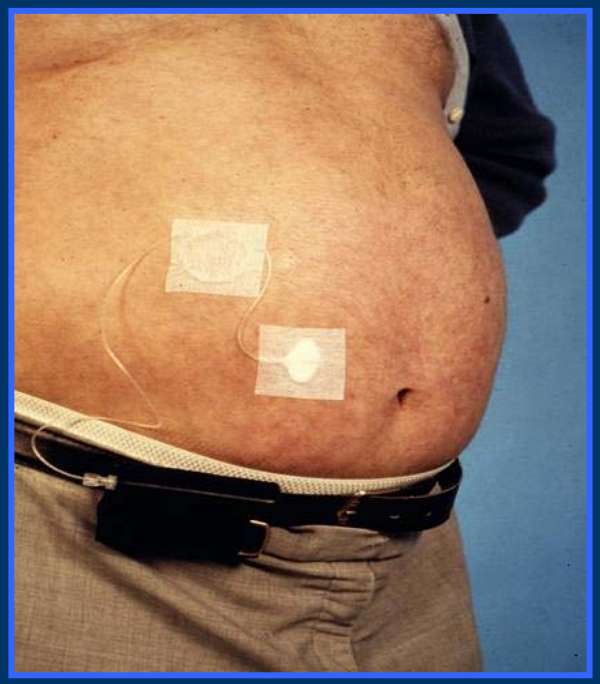

Holst & Deacon, Diabetologia 2005

# Peripheral GLP-1 Reduces Appetite and Food Intake in Man

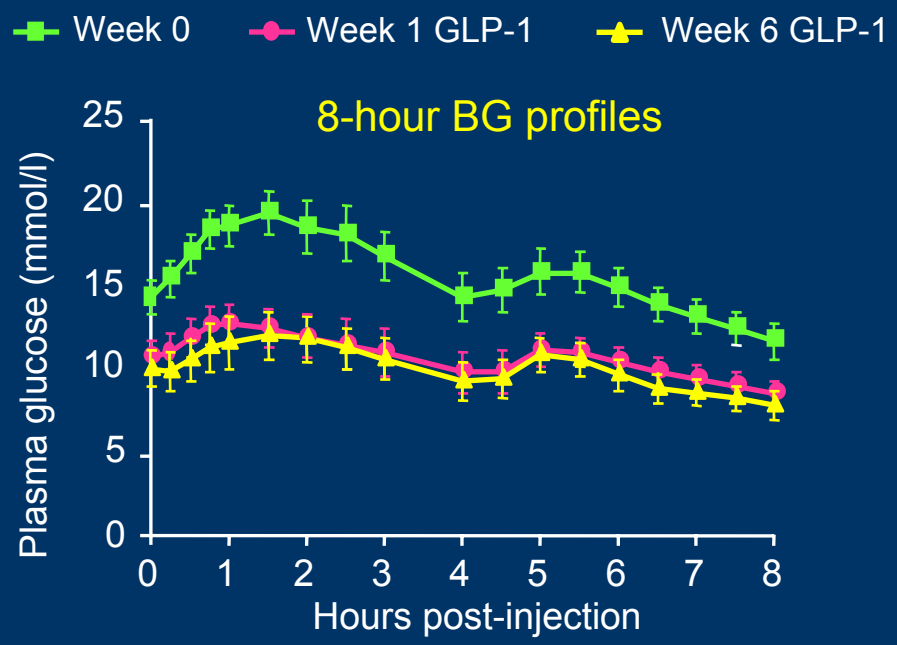


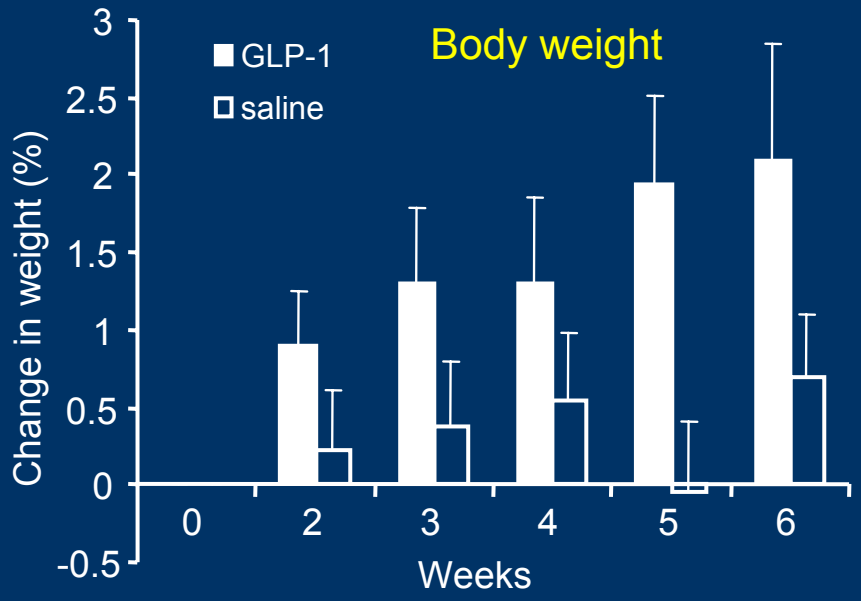

Verdich et al JCEM 2001

# Continuous s.c. Infusion of GLP-1 Reduces Blood Glucose and Lowers Body Weight in Patients with T2DM



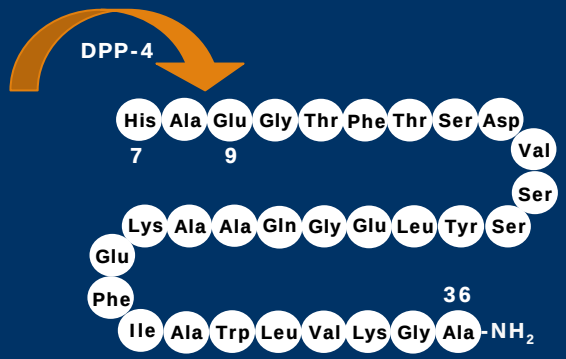
Zander M et al, *Lancet* 2002;359:824-830



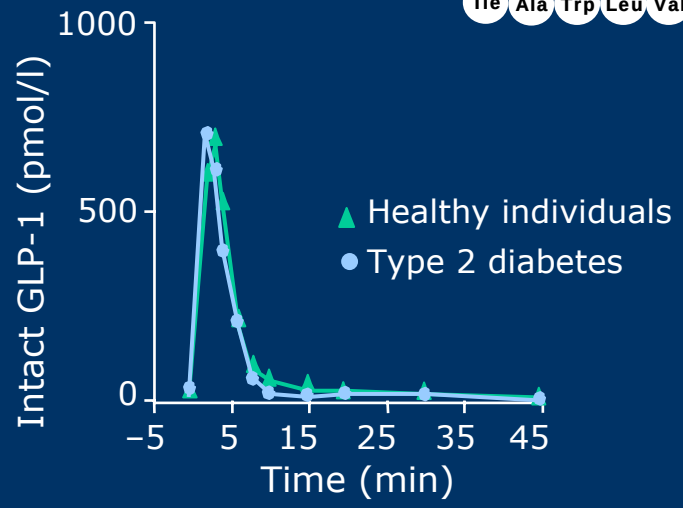



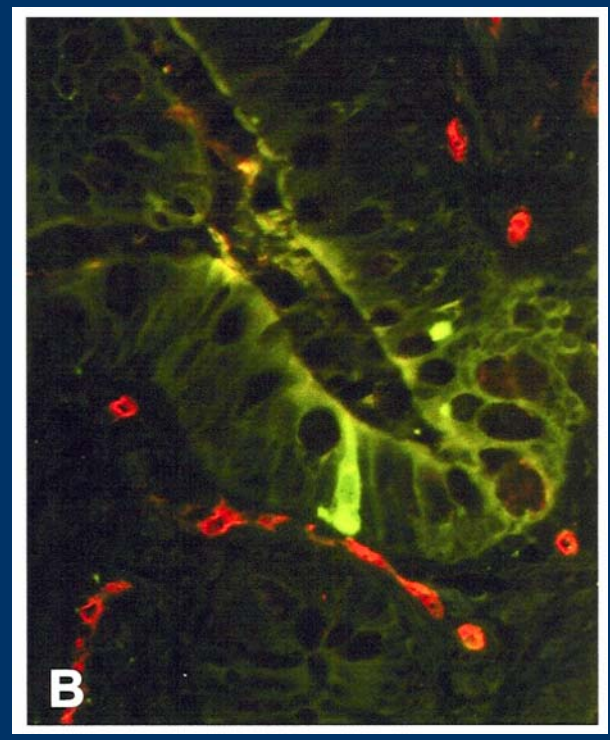
# Harnessing the Potential of GLP-1

# Native GLP-1 has Limited Clinical Potential Because of its Short Half-Life




i.v. bolus GLP-1
(15 nmol)




**DPP-4** and **GLP-1** in human small intestine

Plasma $T_{½}$ =1-2 minutes (i.v.)
MCR = 5-10 l/min

Vilsbøll et al, *JCEM* 2003

Hansen et al, *Endocrinology* 1999

# How has the Therapeutic Potential of GLP-1 been Realised?

- DPP-4 resistant analogues of GLP-1
  (GLP-1 receptor activators; incretin mimetics)

  *Purpose*:
  Raise agonist plasma concentrations into the pharmacological range

- Inhibit DPP-4 activity
  (DPP-4 inhibitors; incretin enhancers)

  *Purpose*:
  Prevent degradation of endogenously released incretin hormones to enhance plasma levels of the active peptides

Deacon et al, *Diabetes* 1995; 44:1126-1131

# Incretin-Based Therapies for Treatment of T2DM

| | Company | Trade name | Status |
|---|---|---|---|
| **GLP-1 analogues (incretin mimetics)** | | | |
| Exenatide | Lilly/Amylin | Byetta | Approved in combination with metformin and/or SU in USA June 2005<br>Approved by EMEA Nov 2006 |
| Liraglutide | Novo Nordisk | | Phase III |
| **DPP-4 inhibitors (incretin enhancers)** | | | |
| Sitagliptin | Merck & Co | Januvia | Approved as monotherapy and in combination with metformin or a TZD in USA October 2006<br>Approved in combination with metformin or TZD by EMEA in April 2007<br>Single tablet combination with metformin approved by FDA in March 2007 |
| Vildagliptin | Novartis | Galvus | Under FDA review<br>Under review by EMEA |

# GLP-1 Receptor Activators
## (Incretin Mimetics)

# Exendin-4


- From saliva of the Gila Monster
- 53% homologous with GLP-1
- Insensitive to DPP-4
- Full agonist at the GLP-1 receptor
- Metabolically stable
  – t½ 4-5 hr after sc injection

Chen & Drucker, J Biol Chem 1997

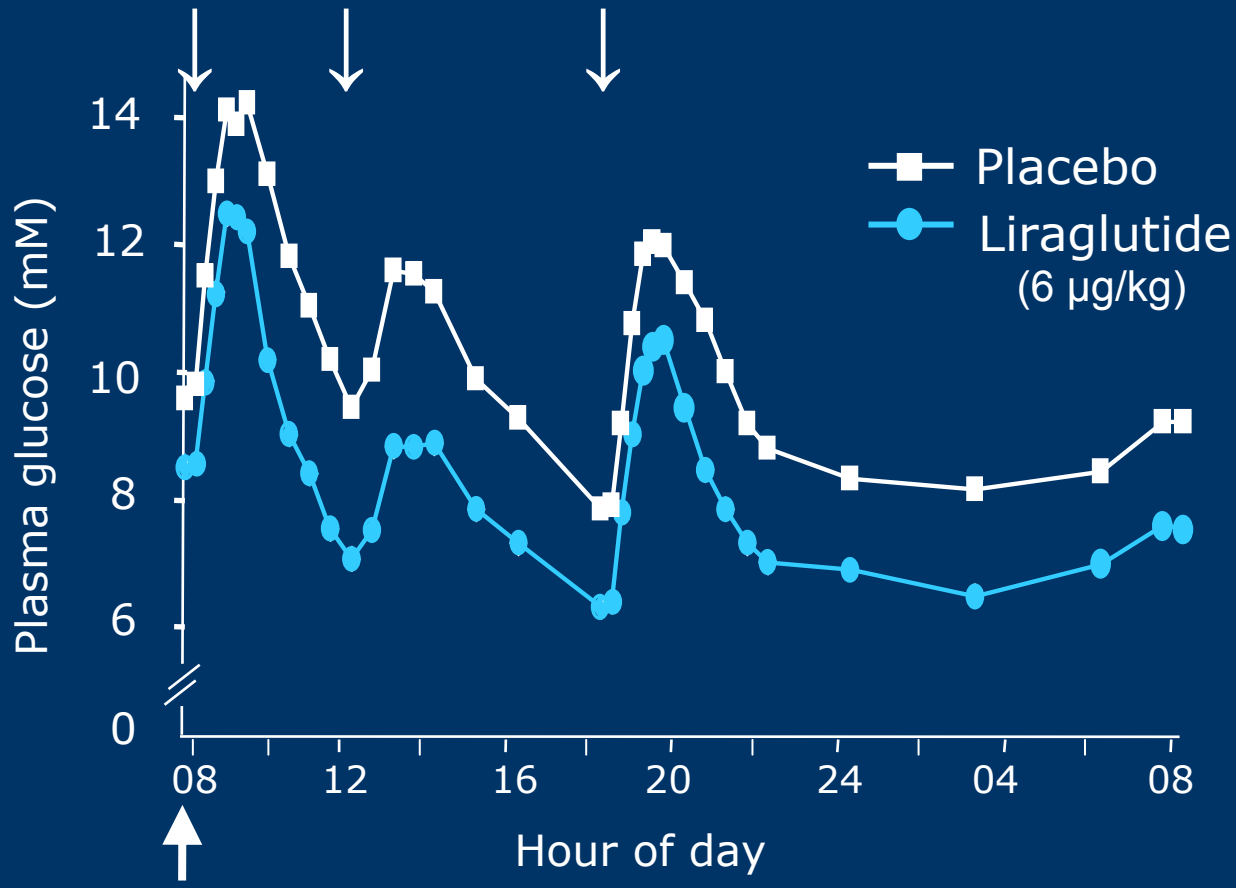
# Liraglutide


- Based on human GLP-1 (7-37)
- 97% homologous with GLP-1
- Resistant to DPP-4
- Full agonist at the GLP-1 receptor
- Non-covalent binding to albumin, self-association, slow release from injection site gives prolonged survival time
  – t½ 12 hr after sc injection

Knudsen et al, J Med Chem 2000

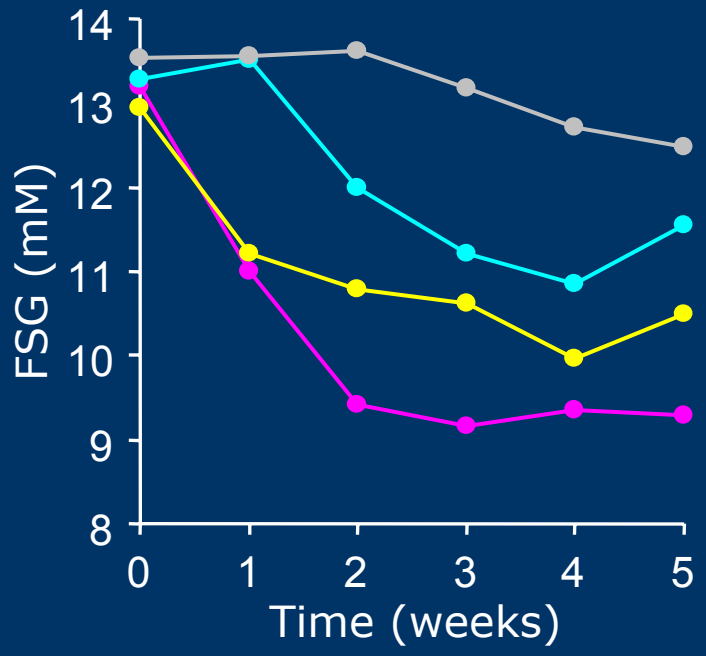
Conserved  Substituted  Additional (relative to human GLP-1 7-37)

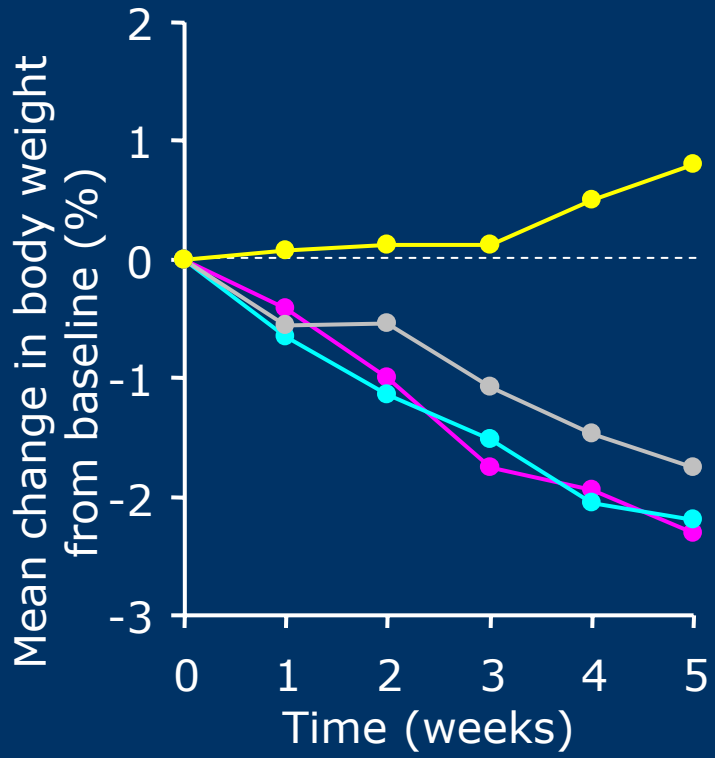
# Incretin Mimetics Reduce 24-h Glucose Profiles in T2DM




Degn et al, Diabetes 2004

# Incretin Mimetics Lower Fasting Plasma Glucose and Body Weight in T2DM



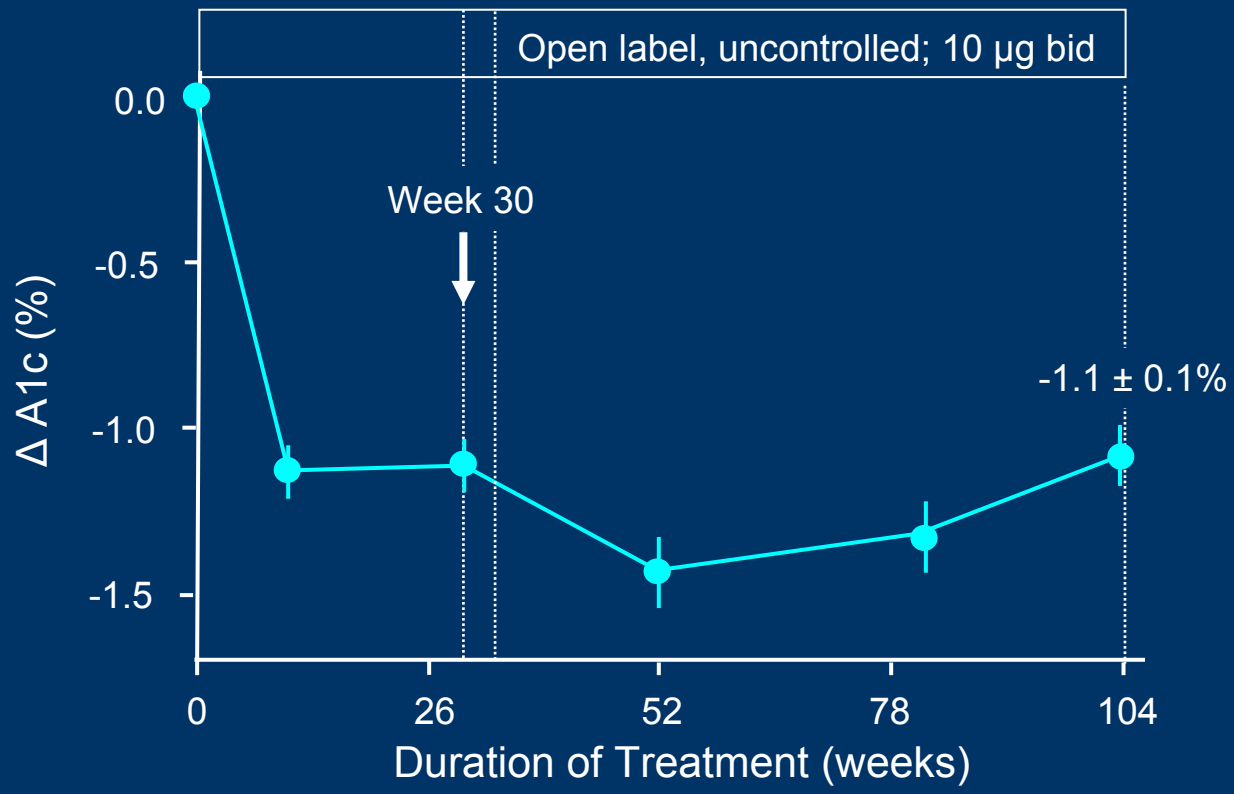




- Metformin (1000 mg bid)
- Liraglutide (0.5 mg totrated to 2 mg qd)
- Metformin + glimepiride (2 mg titrated to 4 mgd)
- Metformin + liraglutide

Nauck et al, Exp Clin Endocrinol Diabetes 2006

# Incretin Mimetics have Sustained Effects on HbA1c

Exenatide add-on to existing OHA; 2 year completer cohort (n=283)

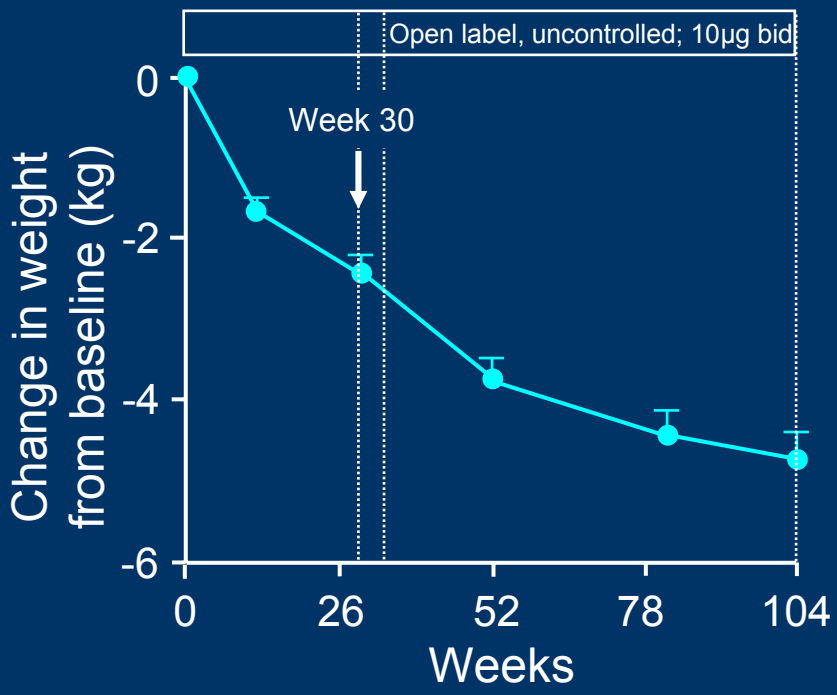


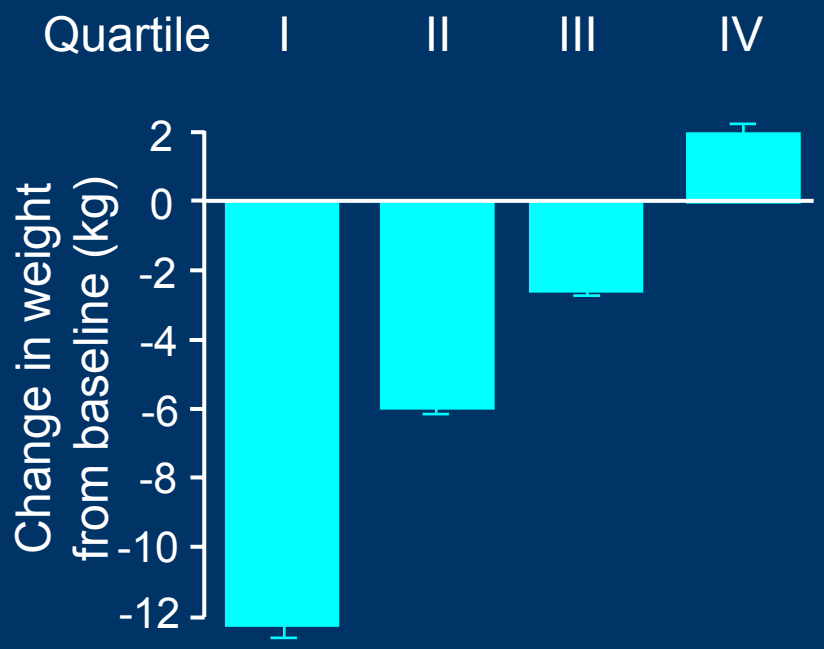

Week 0-30 placebo-controlled trials, 5 or 10 µg bid
Week 30-34 5 µg bid
Week 34 → open label, uncontrolled, 10 µg bid

Buse et al, Clin Ther 2007

# The Majority of Subjects Experience some Weight Loss with Incretin Mimetics

Exenatide add-on to existing OHA; 2 year completer cohort (n=283)




For the entire cohort, mean weight loss was -4.7±0.3 kg (baseline 100 kg)
81% of subjects lost weight

Buse et al, Clin Ther 2007

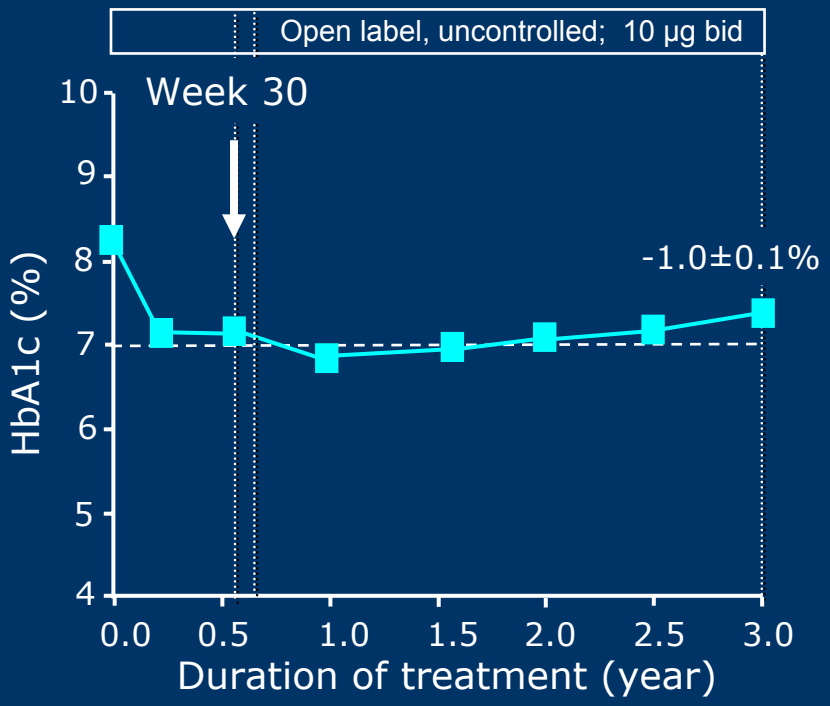
# Incretin Mimetics have Sustained Effects on HbA1c and Body Weight

## HbA1c

Exenatide add-on to existing OHA

3 year completers (n=217)

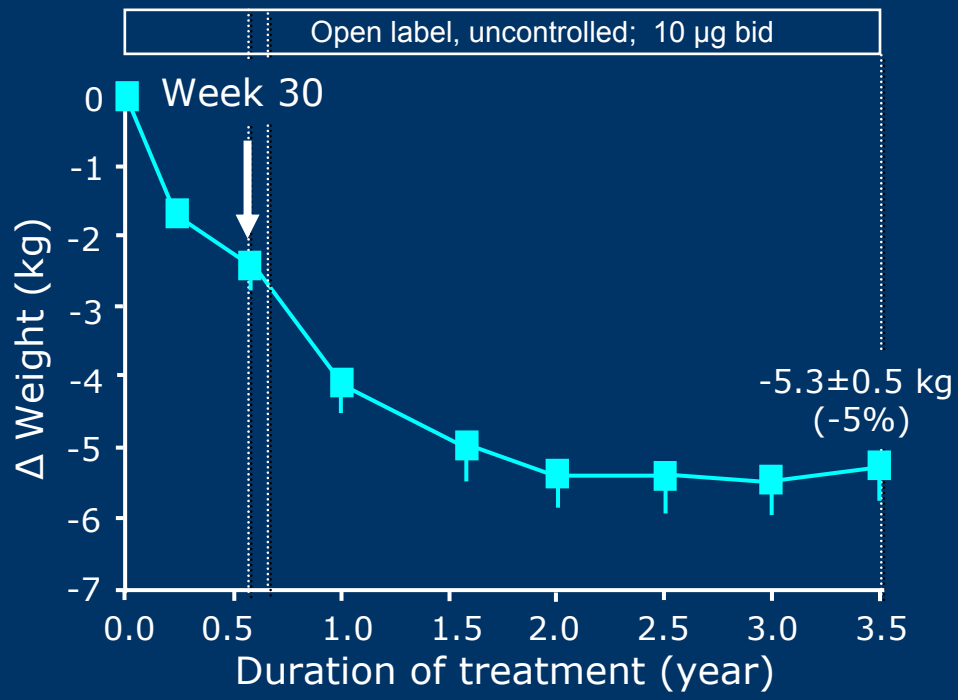
Baseline A1c =8.2%




## Body weight

3.5 year completers (n=151)

Baseline weight =100 kg

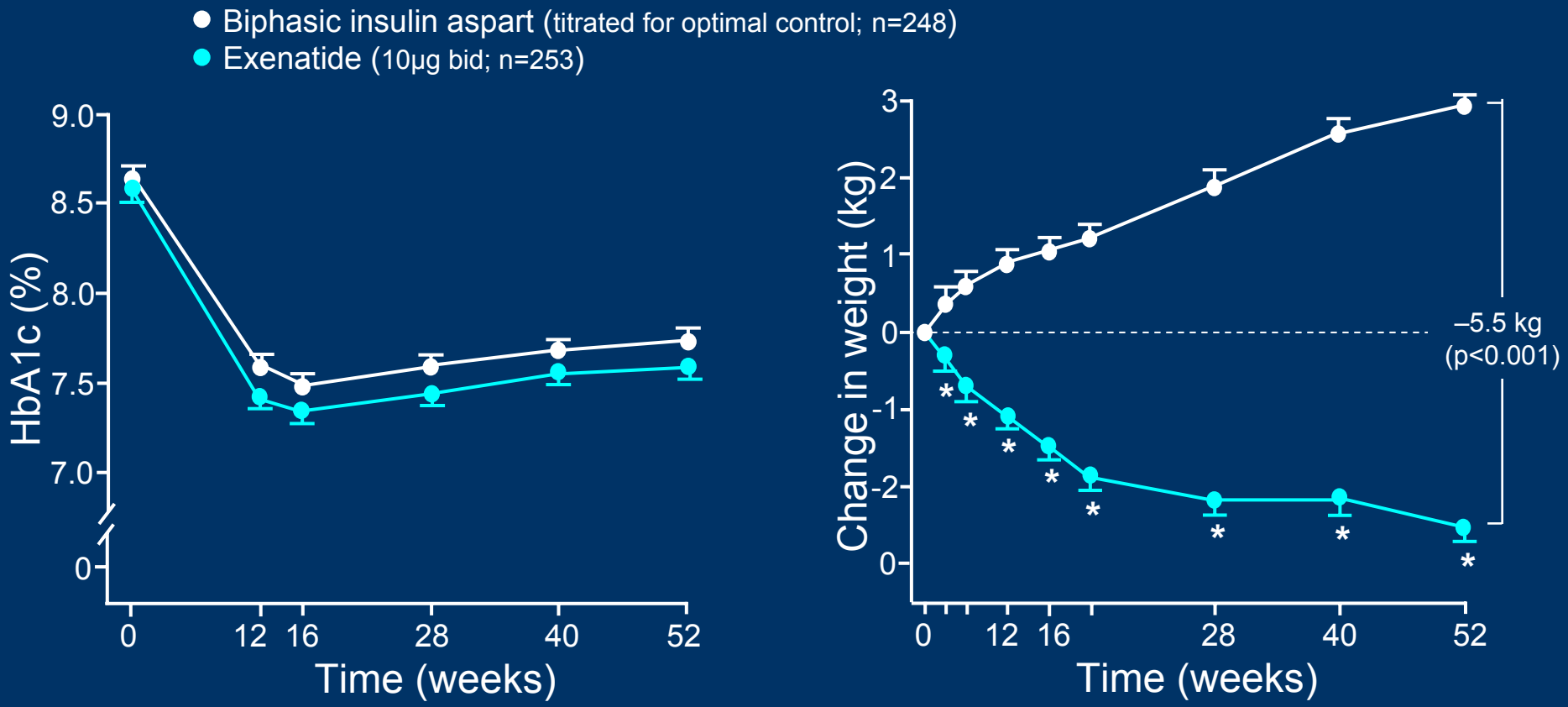



Week 0-30 placebo-controlled trials, 5 or 10 µg bid
Week 30-34 5 µg bid
Week 34 → open label, uncontrolled, 10 µg bid

Nielsen et al, ADA 2007, Poster 0561-P

Kendall et al, ADA 2007, Poster 0557-P

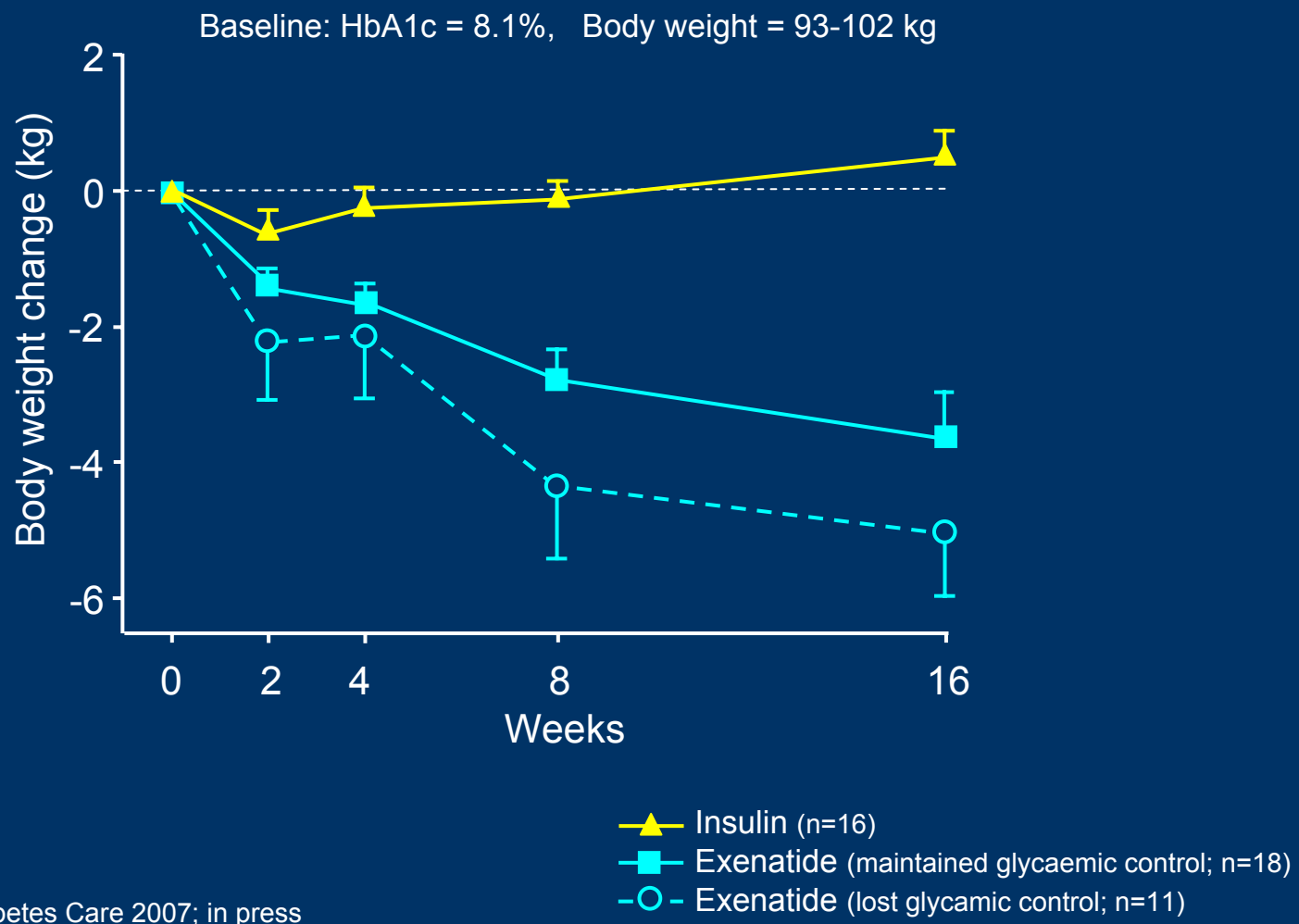
# Incretin Mimetics Lower HbA1c as Effectively as Insulin in Poorly-Controlled SU+Metformin-Treated Patients, but without Body Weight Gain




Baseline weight: ~84.5 kg

Nauck et al, Diabetologia 2007

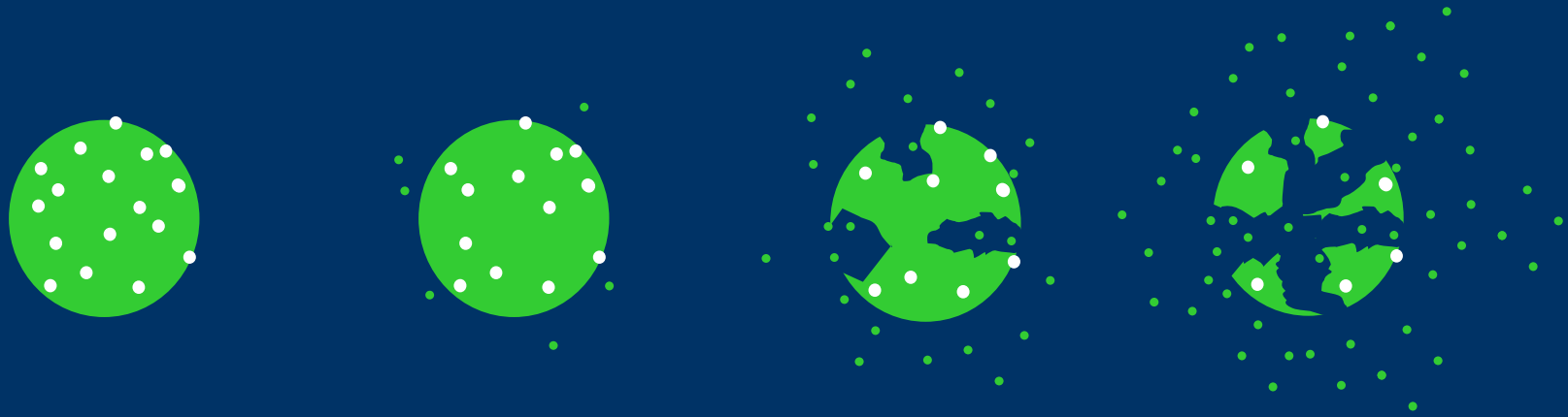
# Patients Treated with Insulin + OHA who Substitute Insulin with Exenatide Maintain Glycaemic Control and Lose Weight




Davis et al, Diabetes Care 2007; in press

# Exenatide Long Acting Release Formulation (Exenatide LAR; phase II)

- biodegradable polymeric microspheres for extended release
- detectable plasma concentrations of exenatide for weeks to months after a single dose



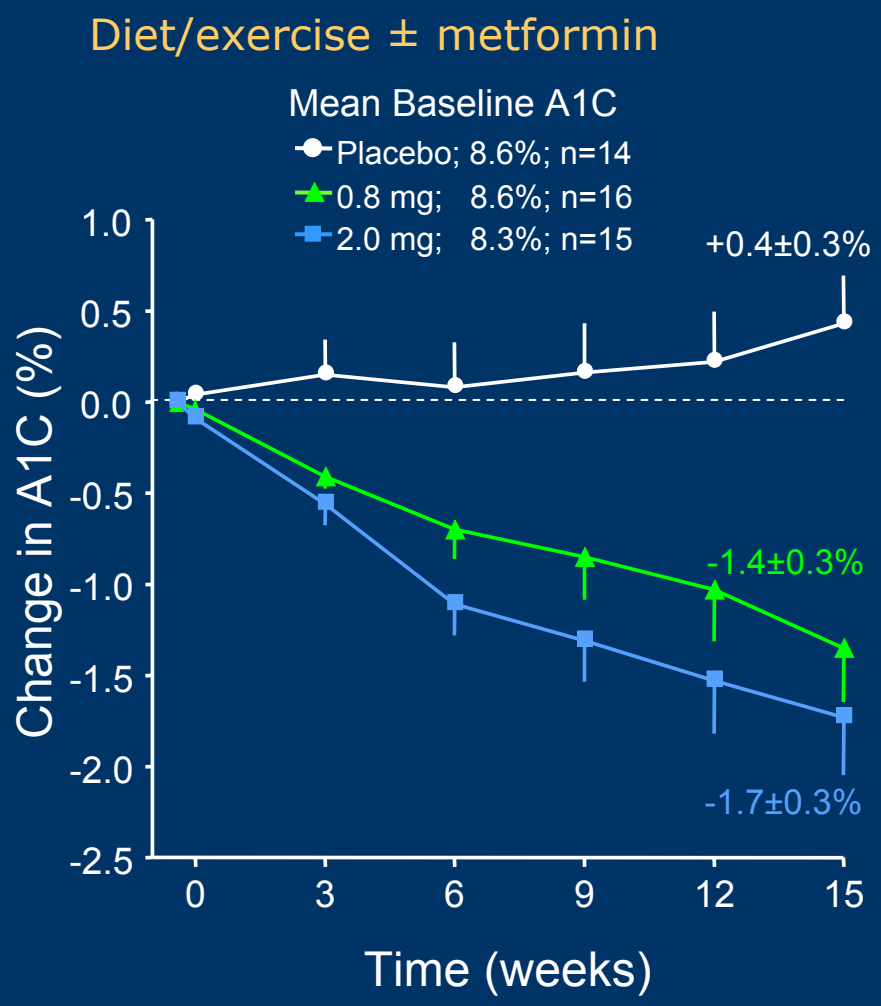
Initial release

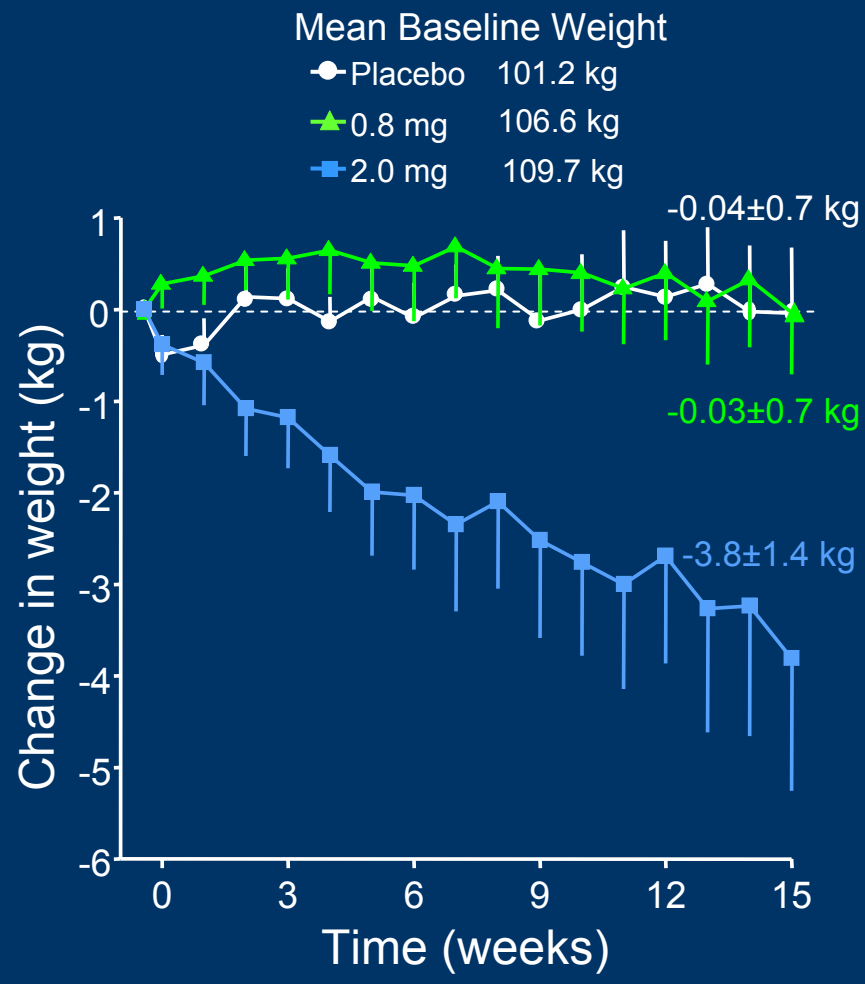
Sustained release

Kim et al. Diabetes Care 2007

# Exenatide LAR Reduces HbA1c and Body Weight after 15 Weeks

Diet/exercise ± metformin




Kim et al. Diabetes Care 2007

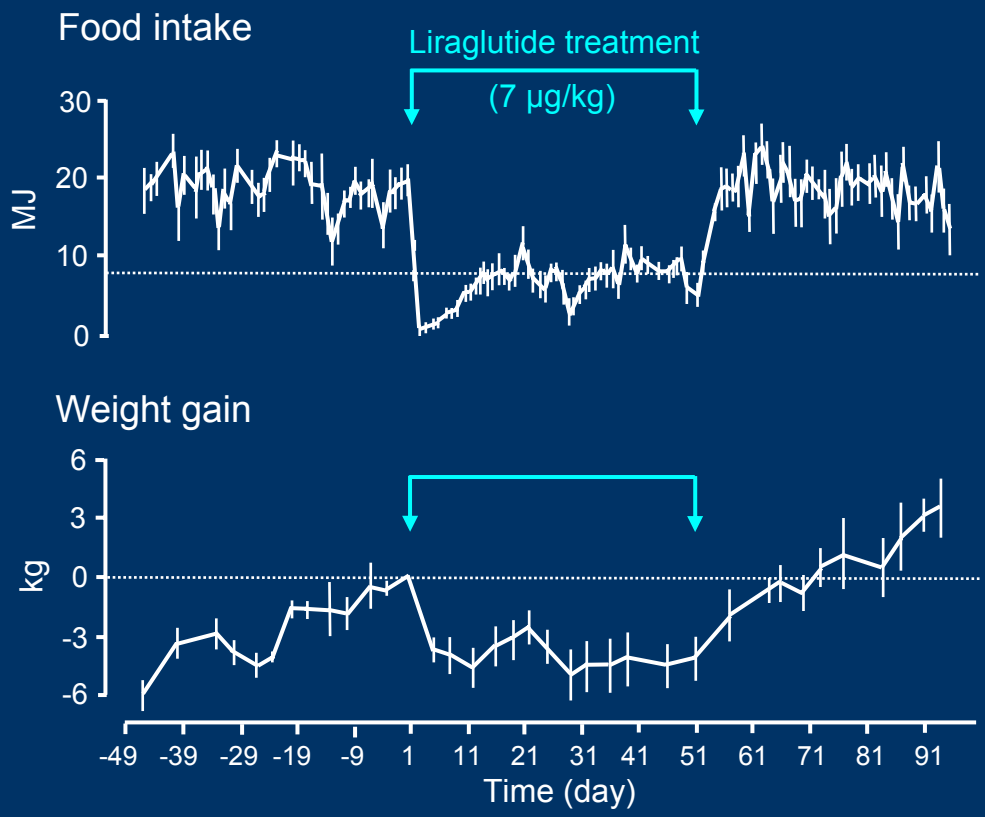
# Summary: GLP-1 receptor activators

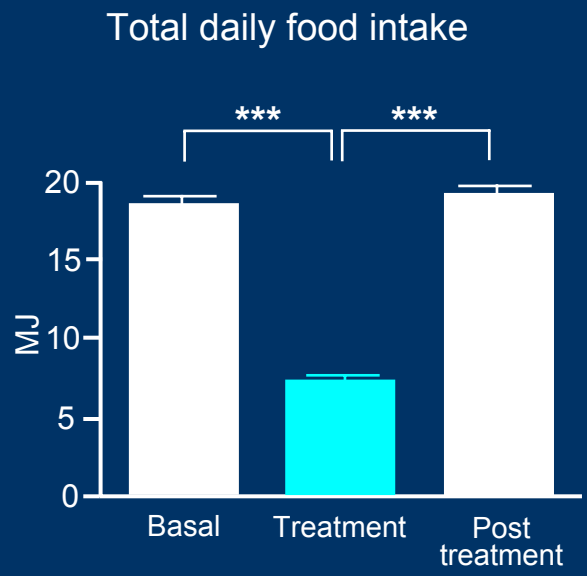
Efficacious

- Glucose-dependent action (enhance insulin, inhibit glucagon secretion)
- Reduce (but do not normalise) blood glucose
- Reduce HbA1c
- Lower body weight
- Differing durations of action (2x daily $\rightarrow$ 1x weekly)
- May cause antibody formation (some)

But, so far, are associated with GI side effects

# Incretin Mimetics Reduce Food Intake and Body Weight Gain in Hyperphagic, Obese, Non-Diabetic Pigs

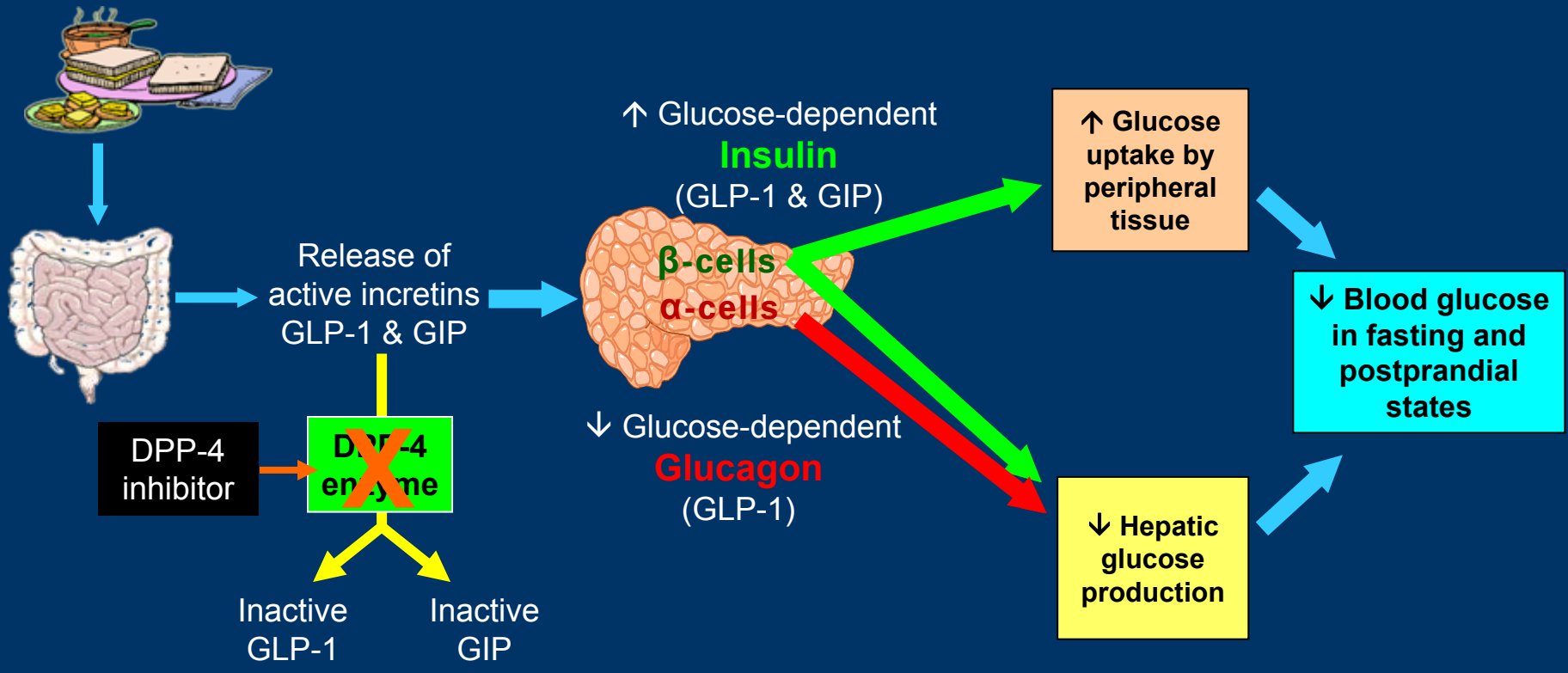



Raun et al, Obesity 2007

# DPP-4 Inhibitors
# (Incretin Enhancers)

# Mechanism of Action of DPP-4 Inhibitors

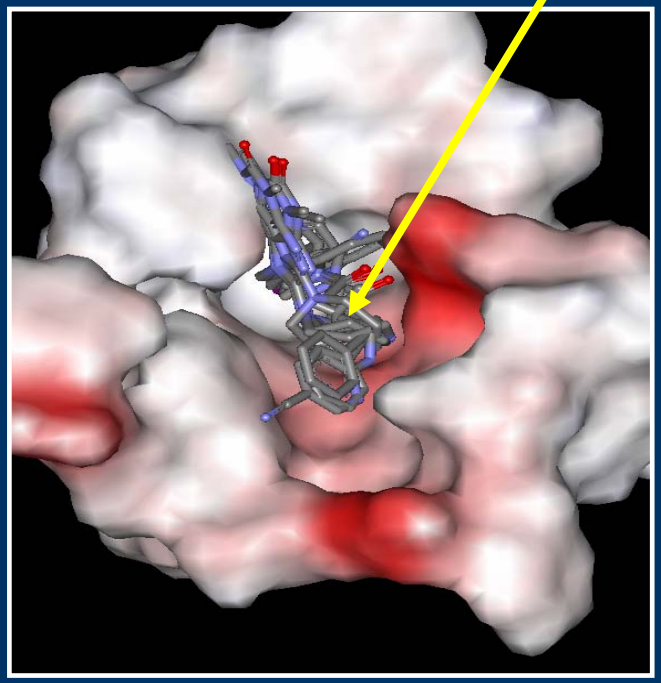



- Incretin hormones GLP-1 and GIP are released by the intestine throughout the day, and their levels ↑ in response to a meal.

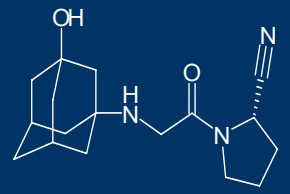
Concentrations of the active intact hormones are increased by DPP-4 inhibition, thereby increasing and prolonging the actions of these hormones.

# DPP-4 Inhibitors Reduce Plasma DPP-4 Activity

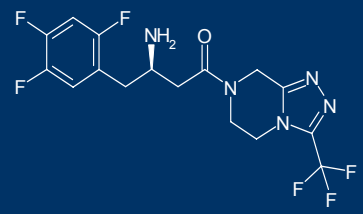
Valine-pyrrolidide
(a prototype DPP-4 inhibitor)

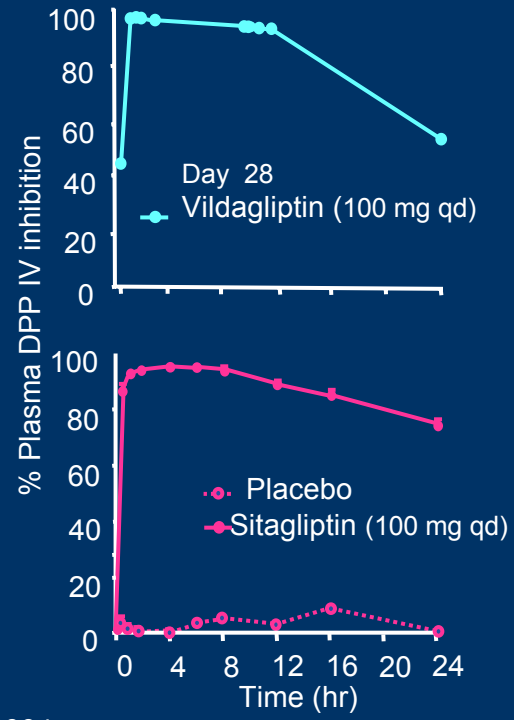


Vildagliptin




Sitagliptin




Ahrén et al, JCEM 2004
Herman et al, Clin Pharmacol Ther 2005

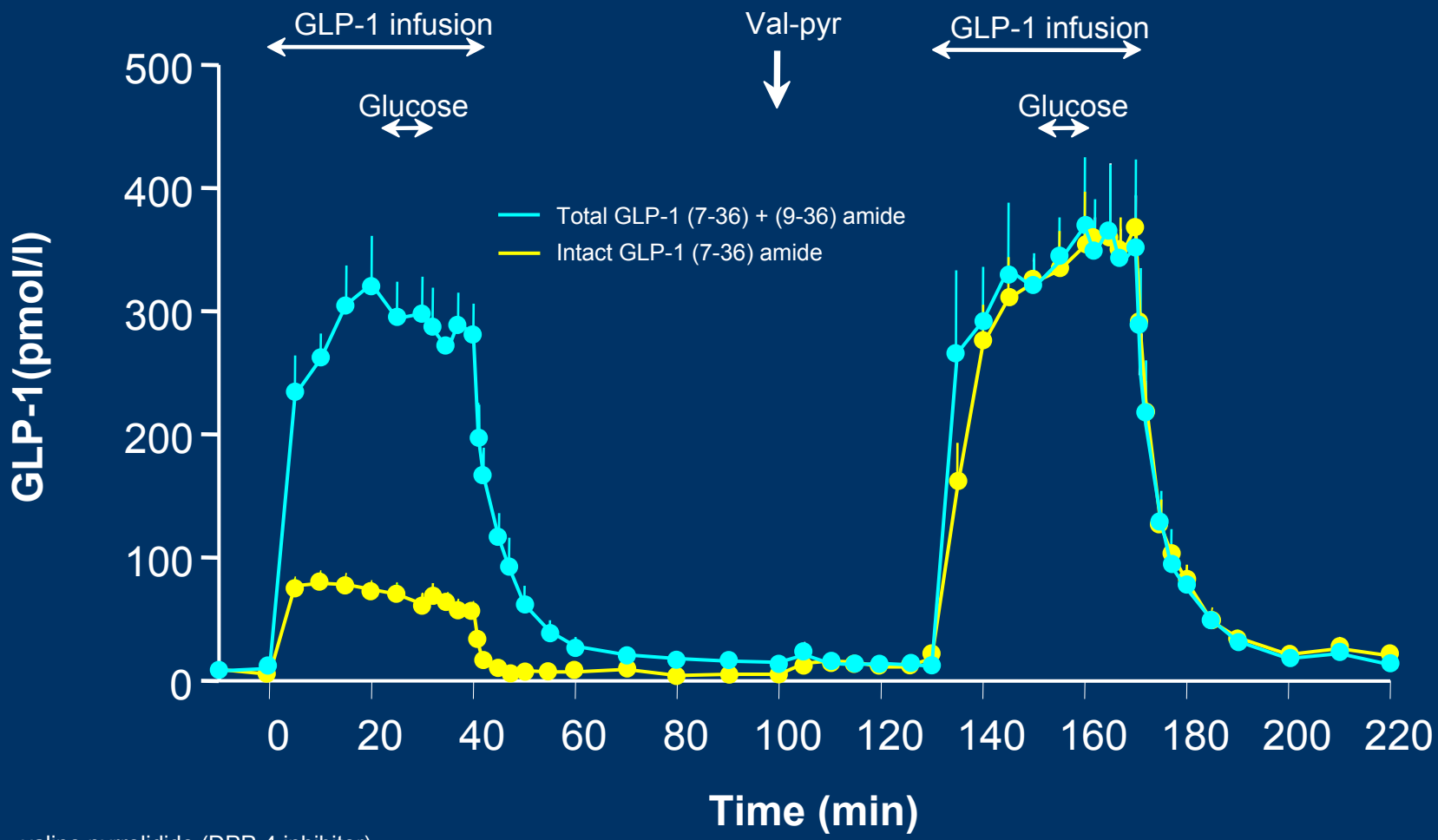
Knowledge of the binding site allow for design of highly selective and potent DPP-4 inhibitors

Rasmussen et al; Nature, 2003

DPP-4 inhibitors in clinical development have different durations of action

- PSN 9301: Short duration of action – meal-related dosing
- Others: Longer duration of action – once daily dosing

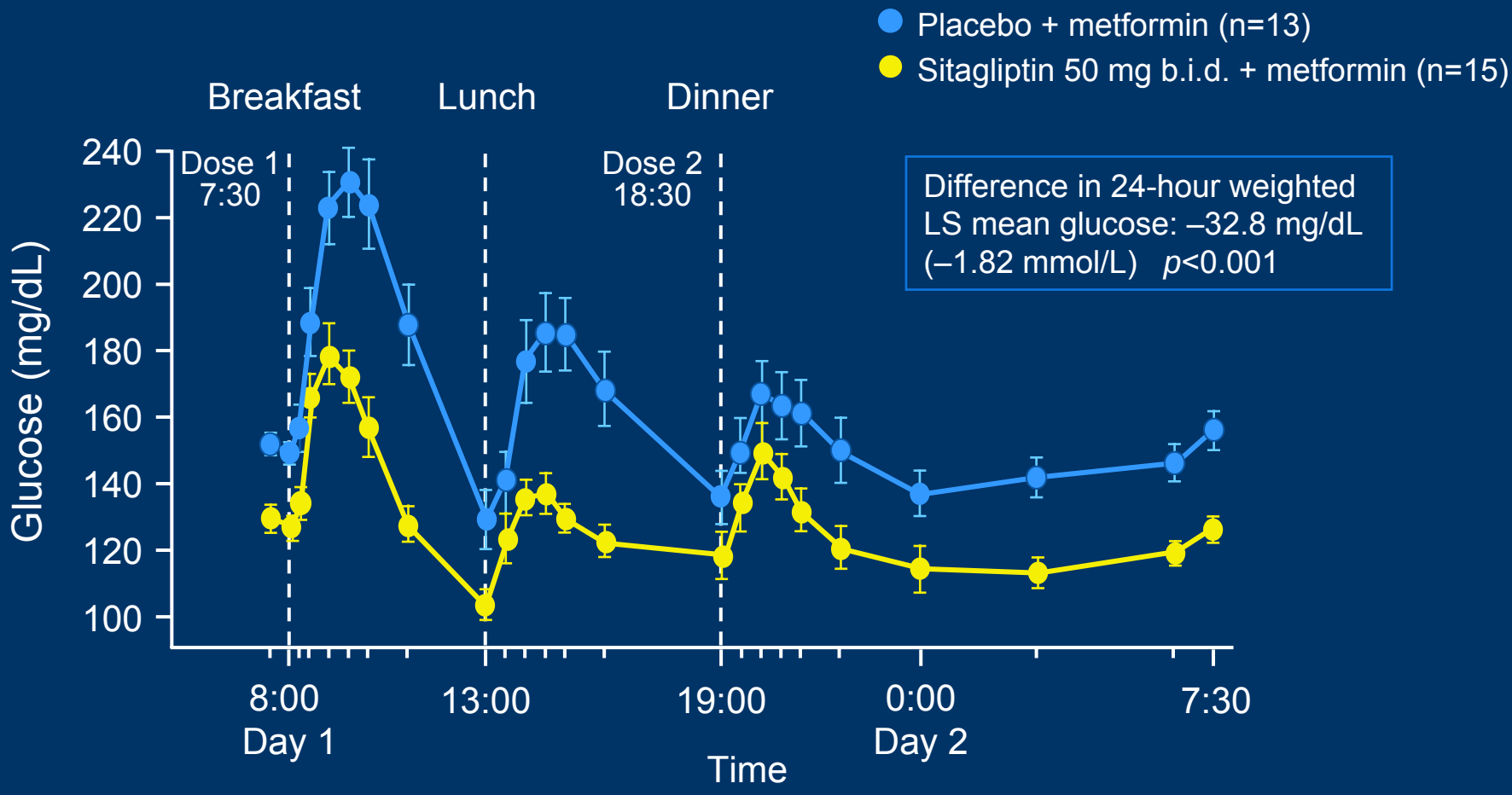
# DPP-4 Inhibition Prevents N-Terminal Degradation of GLP-1 in Anaesthetised Pigs




Val-pyr = valine pyrrolidide (DPP-4 inhibitor)

Deacon et al., Diabetes, 1998

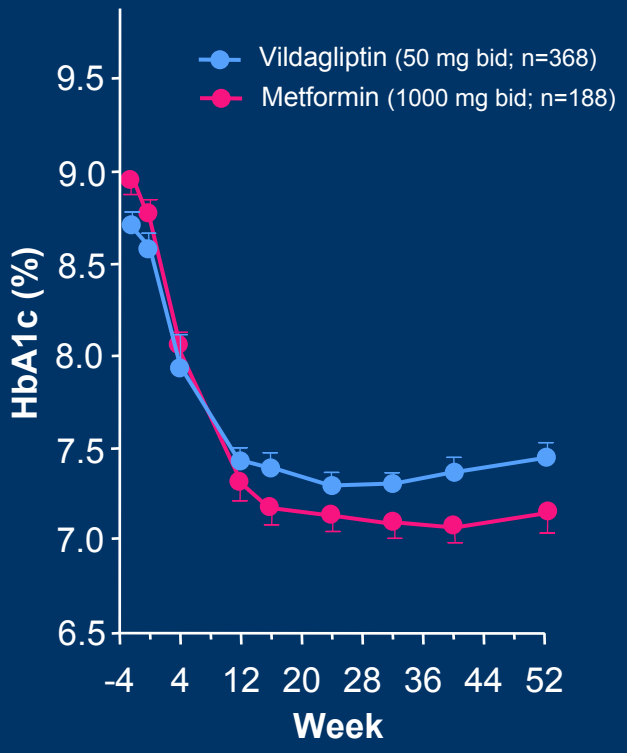
# DPP-4 Inhibition Reduces Both Fasting and Postprandial Glucose Concentrations




Brazg RL et al. Diab Obes Metab 2007

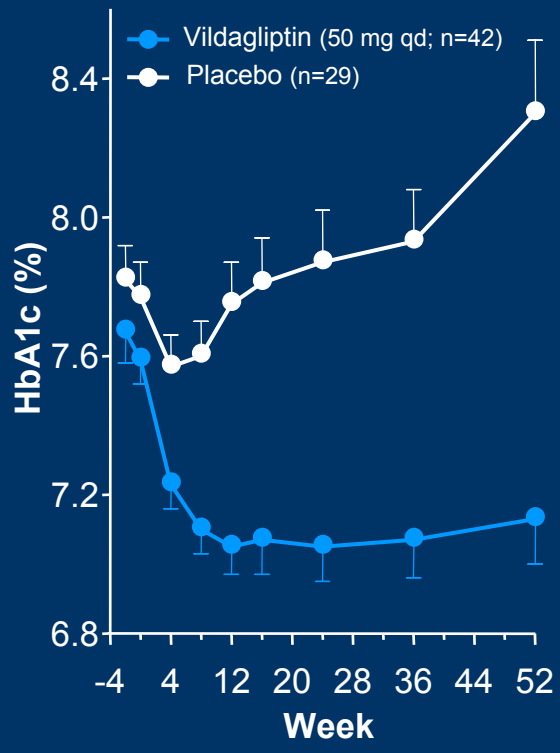
# DPP-4 Inhibitors have Sustained Effects on HbA1c as Monotherapy or as Add-on to Existing OHA in T2DM

Monotherapy

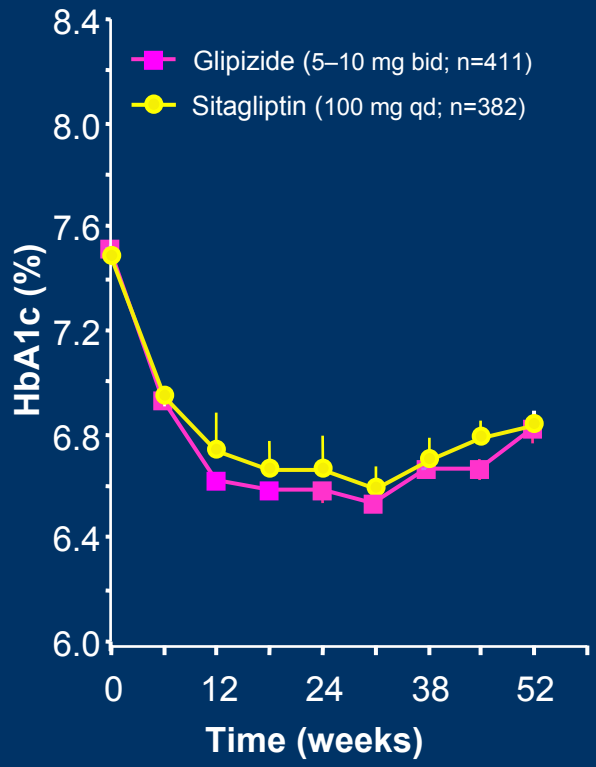



Schweizer et al. Diabetic Med 2004

Add-on to metformin (≥1500 mg/day)



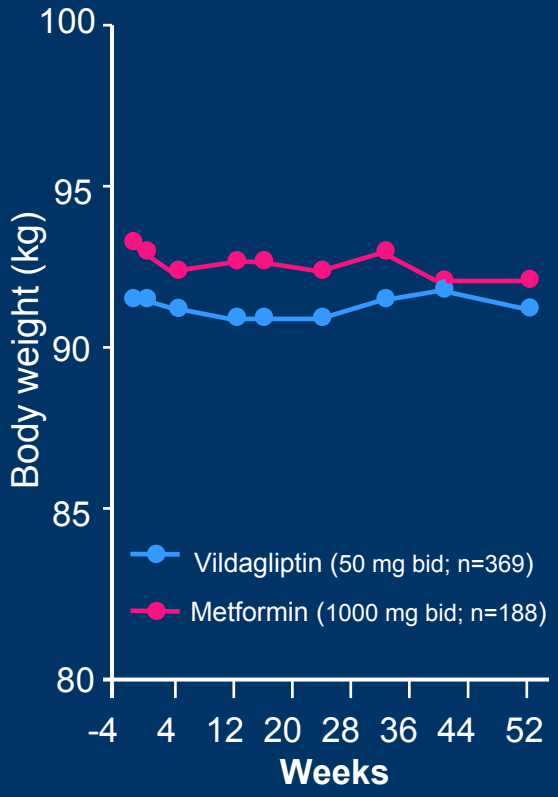

Ahrén et al. Diabetes Care 2004



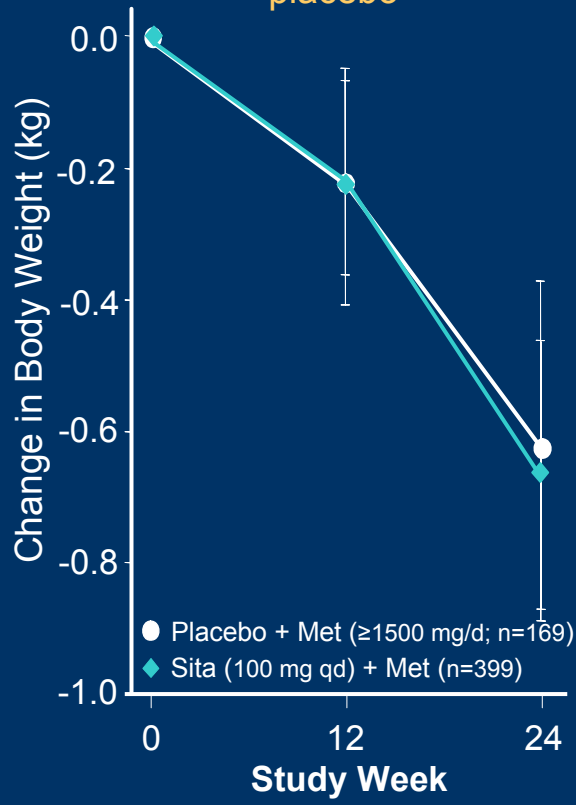

Nauck et al, Diab Obes Metab 2007

# DPP-4 Inhibition is Body Weight Neutral

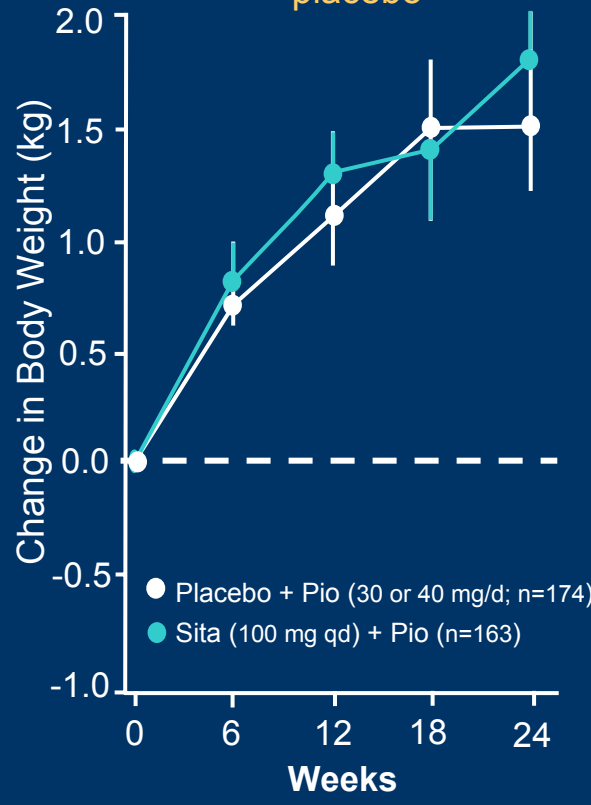
Monotherapy
vs
metformin




Add-on to metformin
vs
placebo




Add-on to pioglitazone
vs
placebo



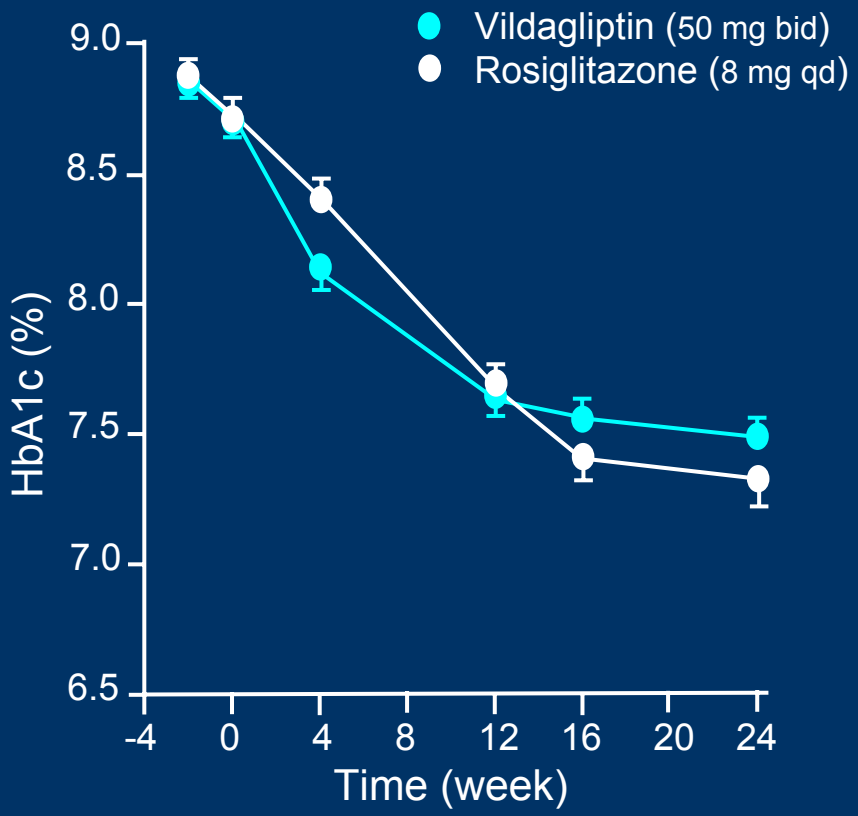

www.novartis.com

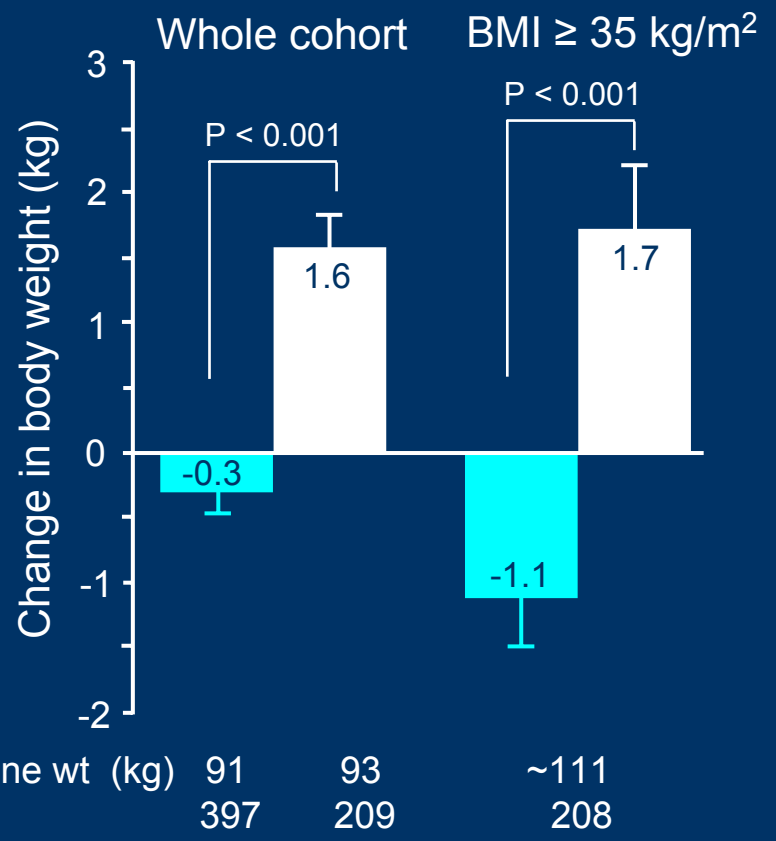
Charbonnel et al, Diabetes Care 2006

Rosenstock et al. Clin Ther 2006

# DPP-4 Inhibition Lowers HbA1c as Effectively as TZD, but without Body Weight Gain

Monotherapy

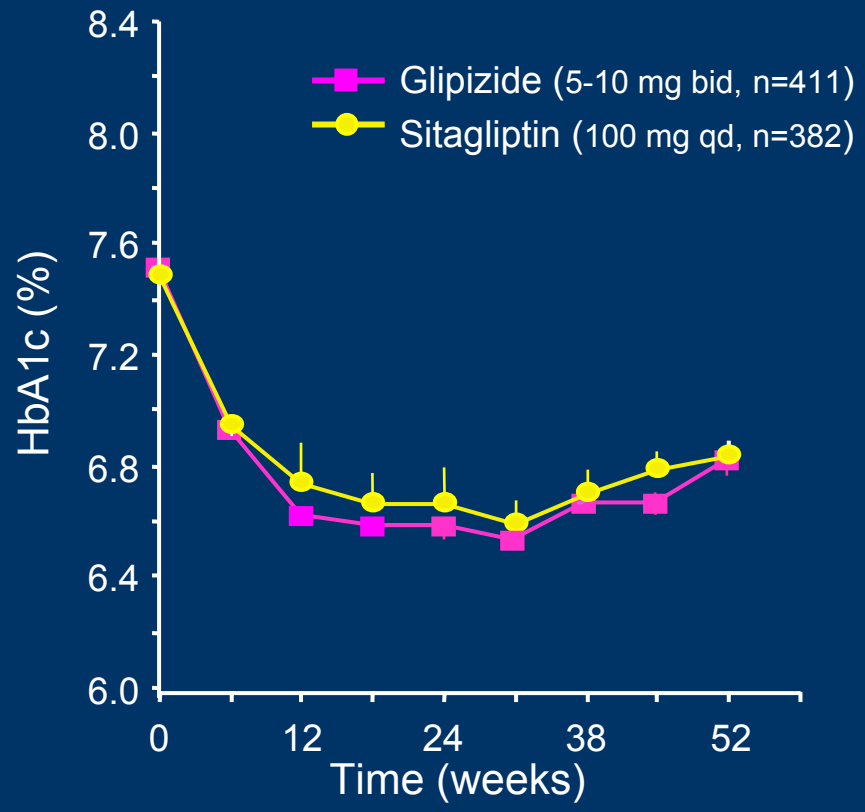


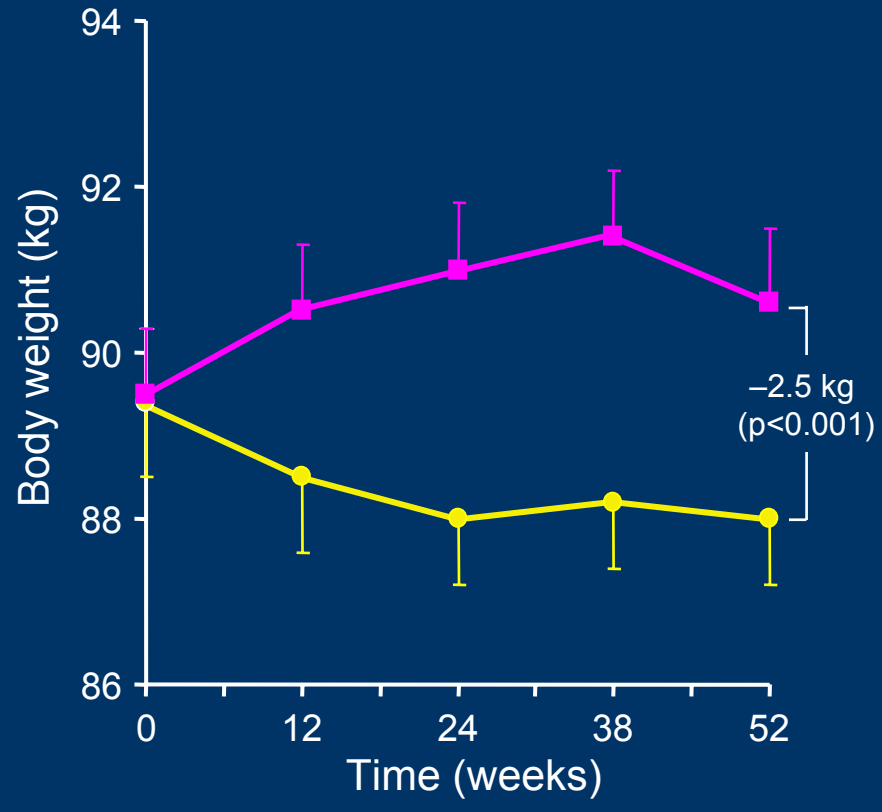




Rosenstock et al Diabetes Care 2007

# DPP-4 Inhibition Lowers HbA1c as Effectively as SU, but without Body Weight Gain

Add-on to metformin (≥1500 mg/day)




Nauck et al, Diab Obes Metab 2007

# Summary: DPP-4 inhibitors

Efficacious

- Glucose-dependent action (enhance insulin, inhibit glucagon secretion)
- Reduce (but do not normalise) blood glucose
- Reduce HbA1c
- Body weight neutral
- Little to distinguish between them clinically

Well tolerated (side effect profile similar to placebo)

# Conclusions

- An incretin-based therapy of type 2 diabetes may be expected to
  - Reduce hyperglycaemia and HbA1c levels without weight gain
  - Reduce appetite and lower body weight (mimetics only)
  - Improve α-cell and β-cell function
  - Improve insulin sensitivity (secondary to improved metabolic control)
  - Combine well with existing antihyperglycaemic agents
  - Be efficacious without side effects
- Incretin mimetics may additionally have a role in obesity treatment