Le incretine: un passo avanti

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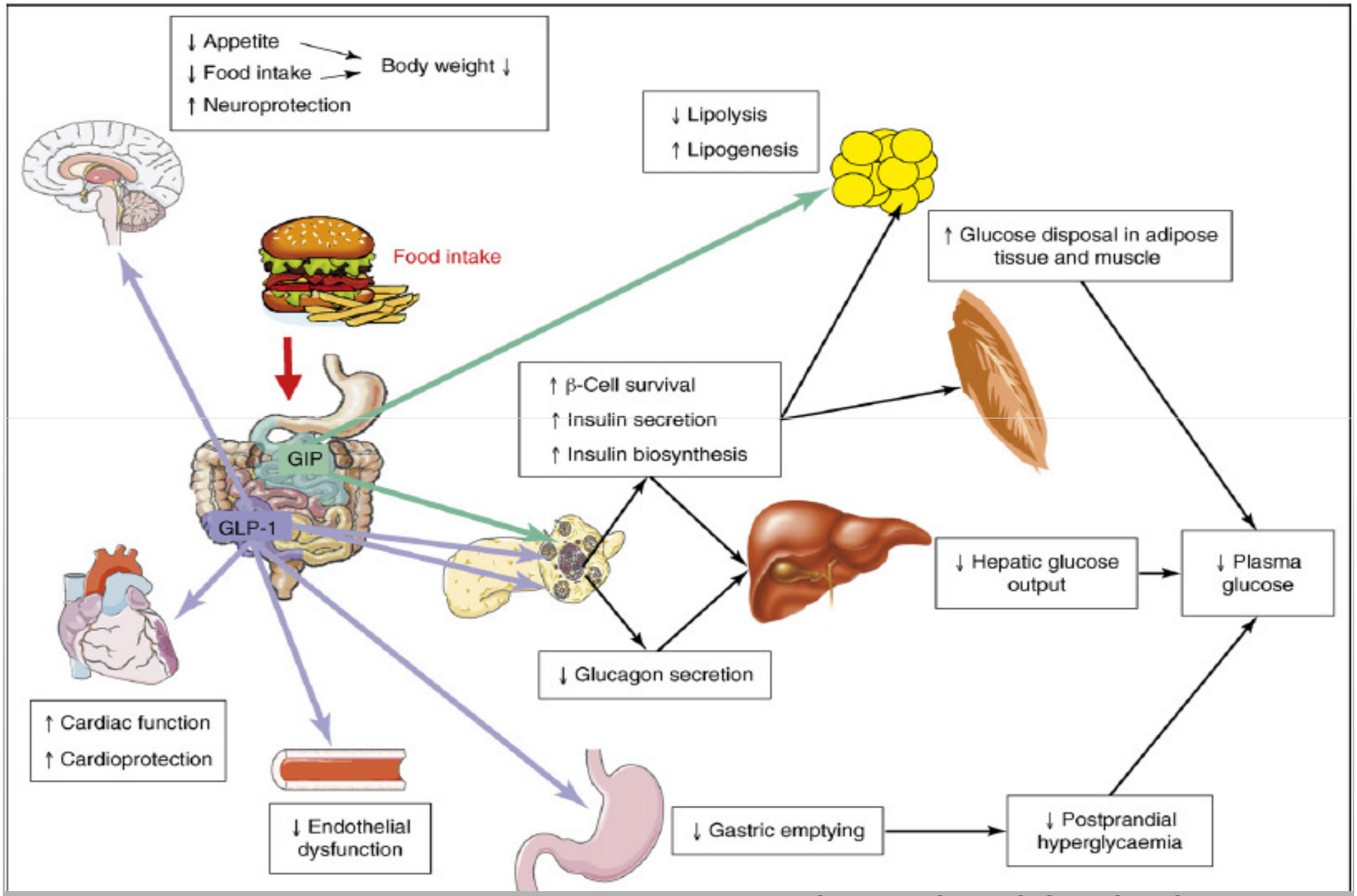
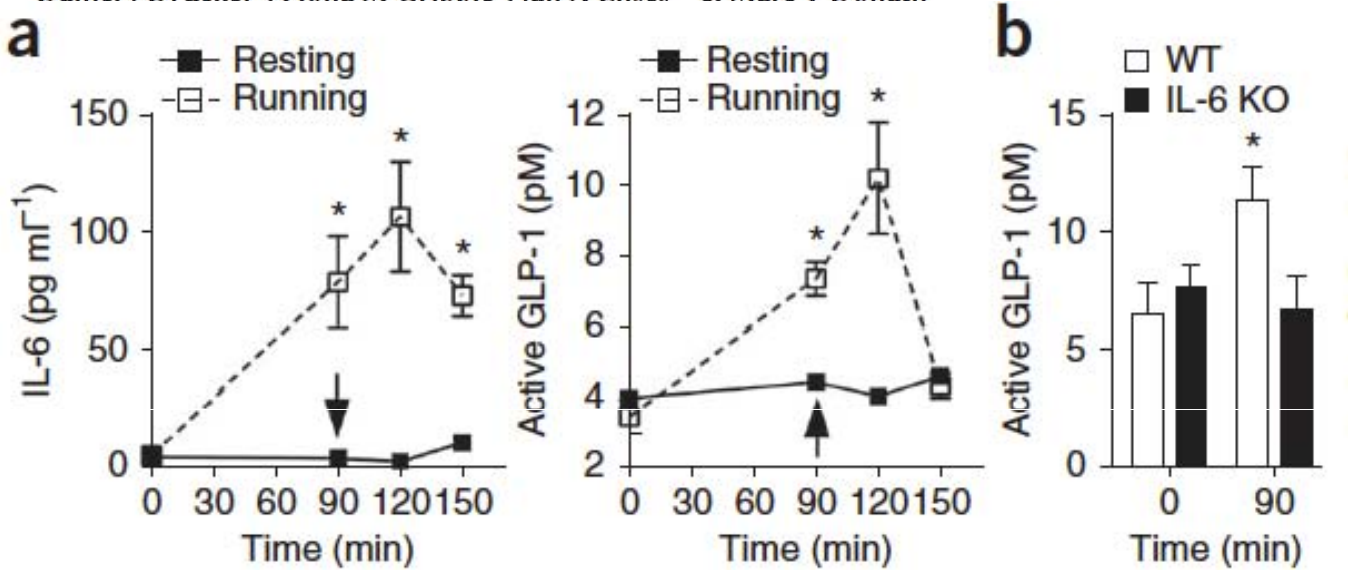
Incretins: multiple targets – multiple actions

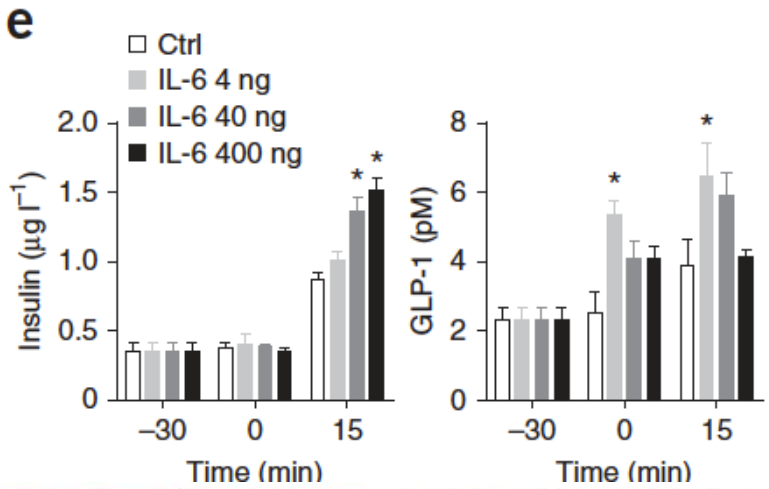


Holst JJ et al Trends in Mol Med 2008

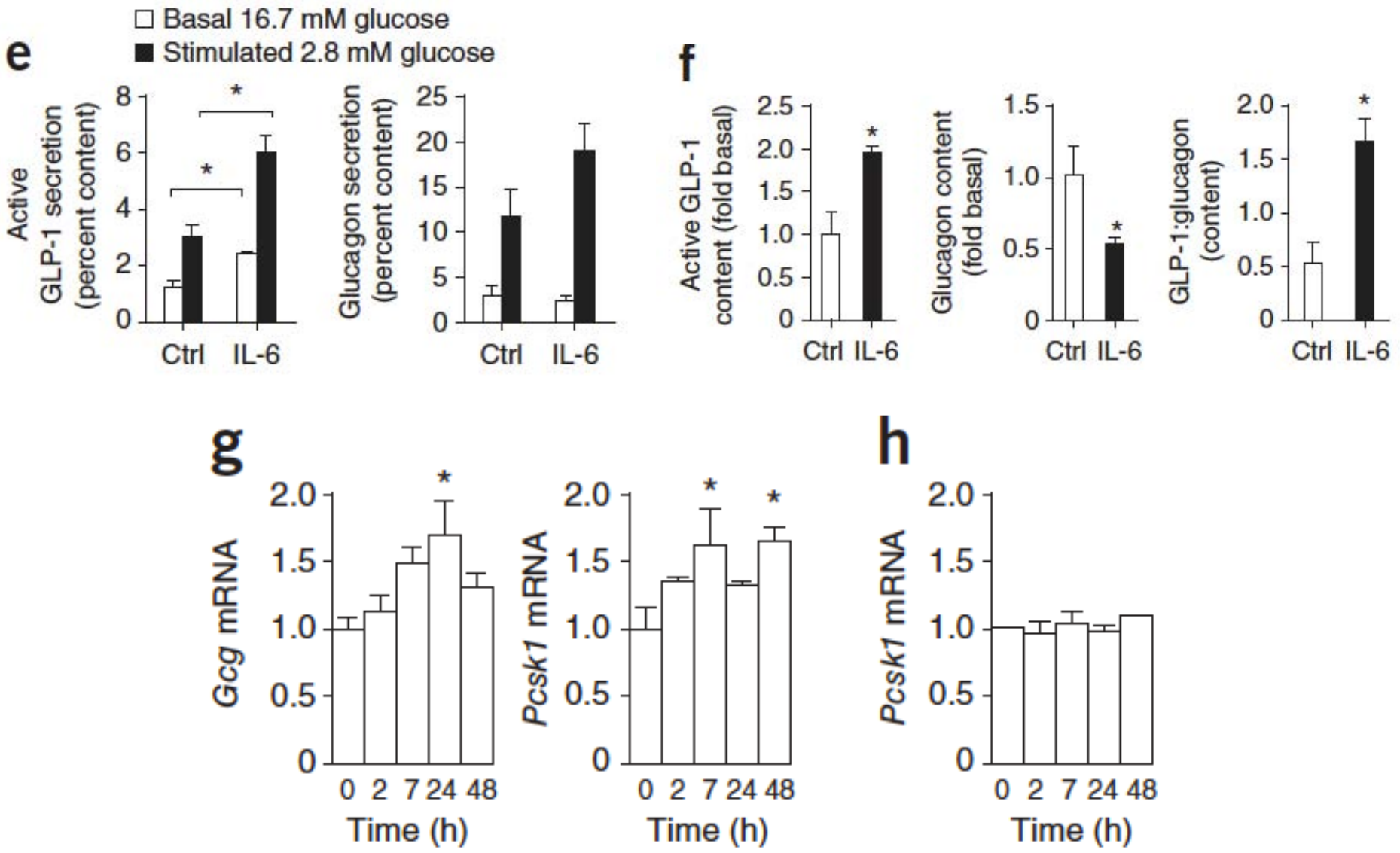
Interleukin-6 enhances insulin secretion by increasing glucagon-like peptide-1 secretion from L cells and alpha cells

Helga Ellingsgaard[1], Irina Hauselmann[1], Beat Schuler[2], Abdella M Habib[3], Laurie L Baggio[4], Daniel T Meier[1], Elisabeth Eppler[5], Karim Bouzakri[6], Stephan Wueest[7], Yannick D Muller[8], Ann Maria Kruse Hansen[9], Manfred Reinecke[5], Daniel Konrad[7], Max Gassmann[2], Frank Reimann[3], Philippe A Halban[6], Jesper Gromada[10], Daniel J Drucker[4], Fiona M Gribble[3], Jan A Ehses[11] & Marc Y Donath[1]

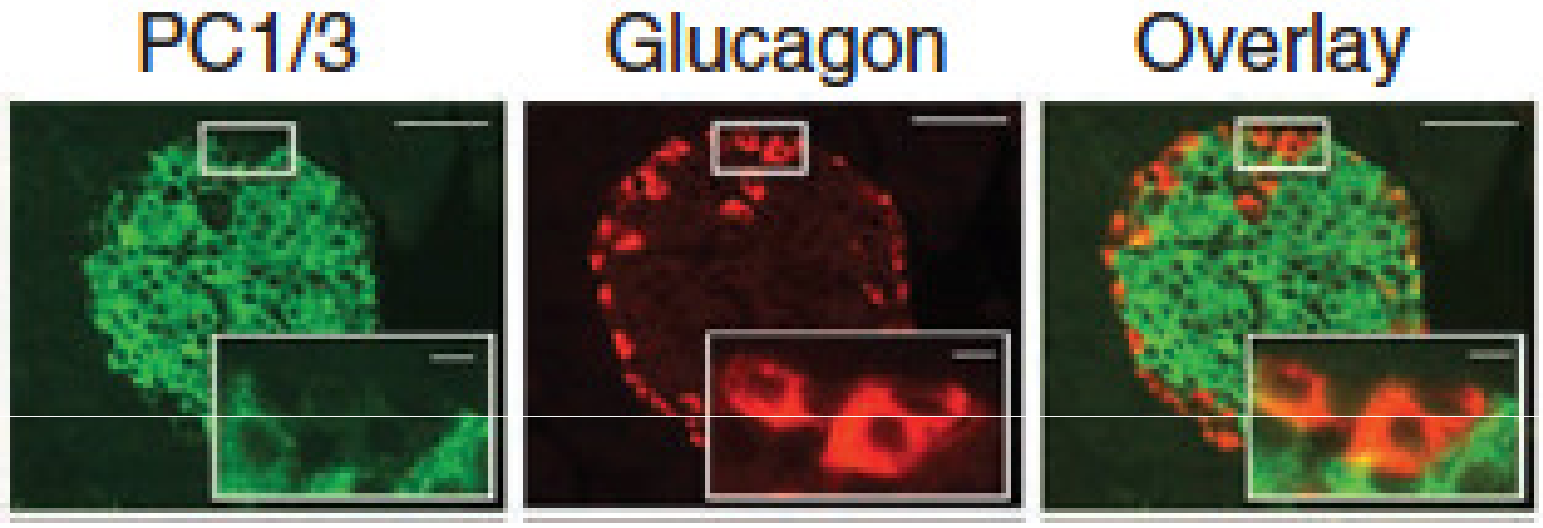




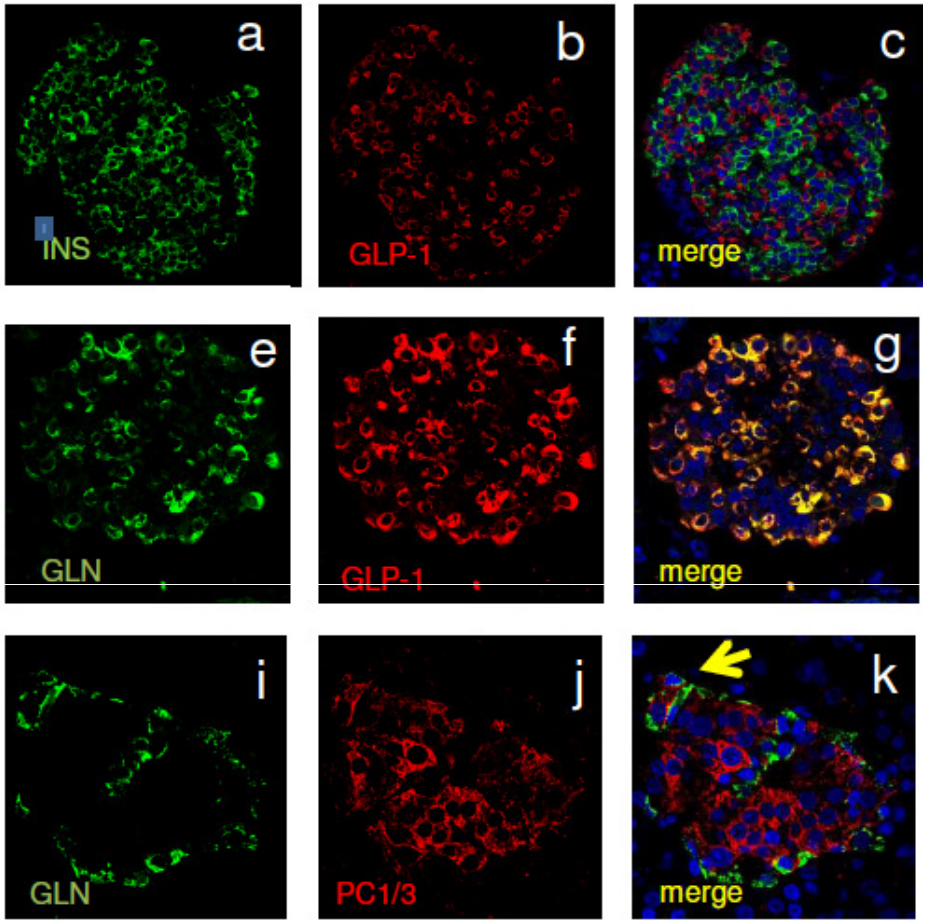
IL-6 stimulates GLP-1 secretion in human islets and alpha cells

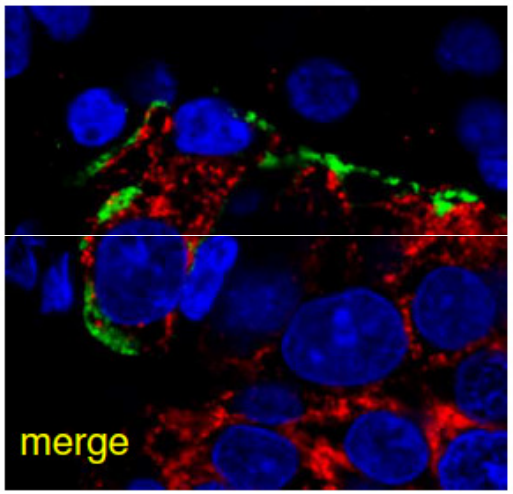


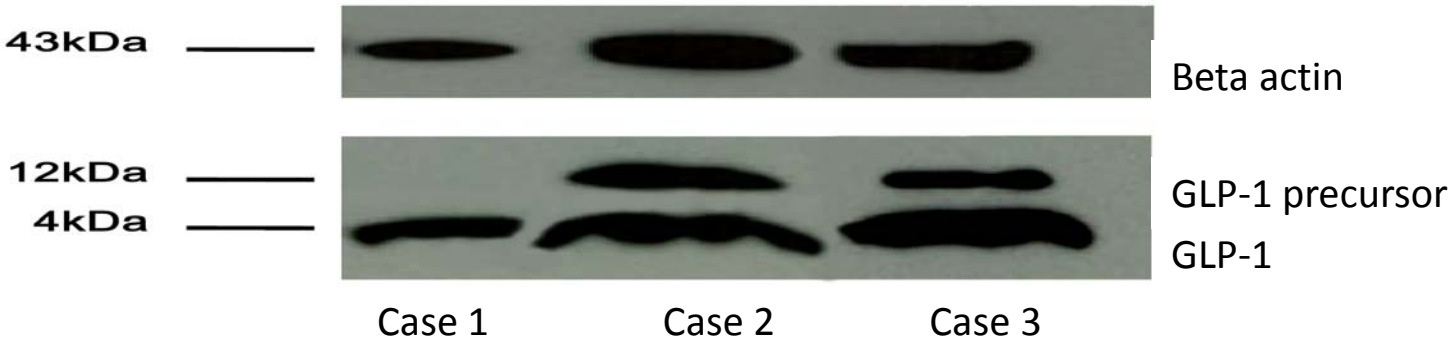
PC1/3 expression in murine alpha cells



GLP-1 and PC1/3 expression in human alpha cells







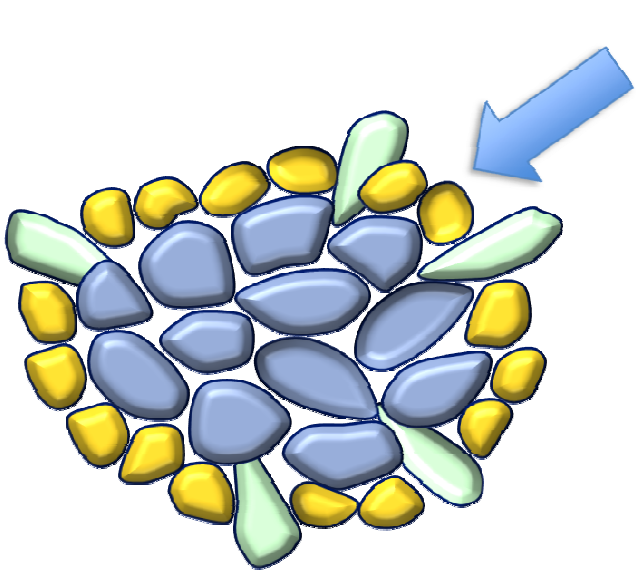
GLP-1 secretion by human islets

Insulin secretion

Glucagon secretion

Somatostatin secretion

GLP-1 secretion



Sitagliptin

Vildagliptin

Saxagliptin

Linaglitpin

Pancreatic cells: β-cell α-cell δ-cell

LIRAGLUTIDE

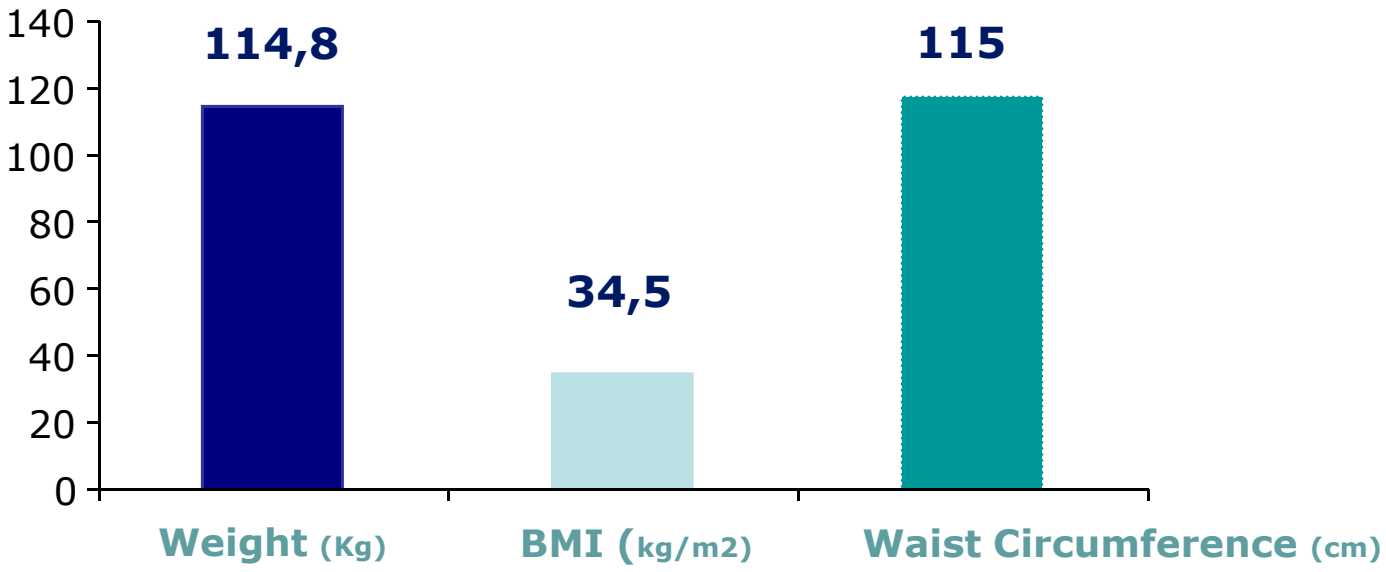
Sesso	N. pazienti	%	Età media (Min - Max)
Maschi	12552	51.7	58 (18 - 94)
Femmine	11712	48.3	59 (18 - 96)
Totale	**24264**	**100.0**	**59 (18 - 96)**

Classe di età	Maschi		Femmine	
	N.	%	N.	%
18-45	1399	53.1	1237	46.9
46-60	5912	53.1	5217	46.9
61-75	4846	50.3	4782	49.7
>75	395	45.4	476	54.6
Totale	**12552**	**51.7**	**11712**	**48.3**

Pts <60 yrs are 57.0 % of the total

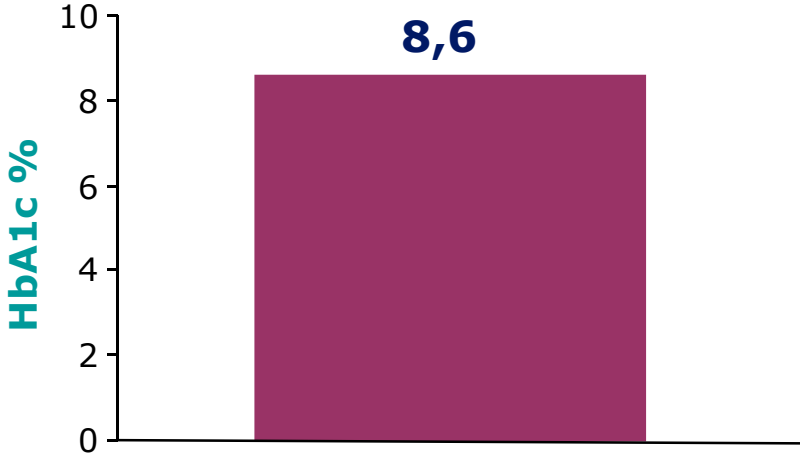
Liraglutide data: baseline clinic parameters

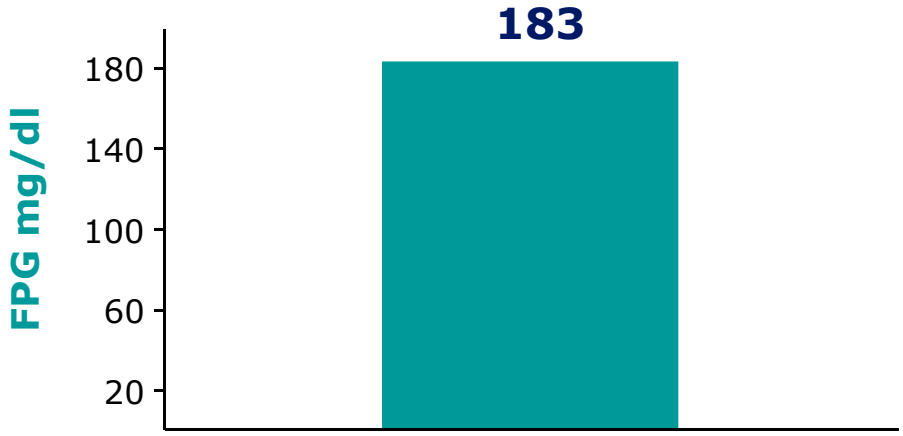
Pts: 24140 with clinical data included (data are means)



Liraglutide data: baseline clinic parameters

Pts. 24140 with clinical data included (data are means)



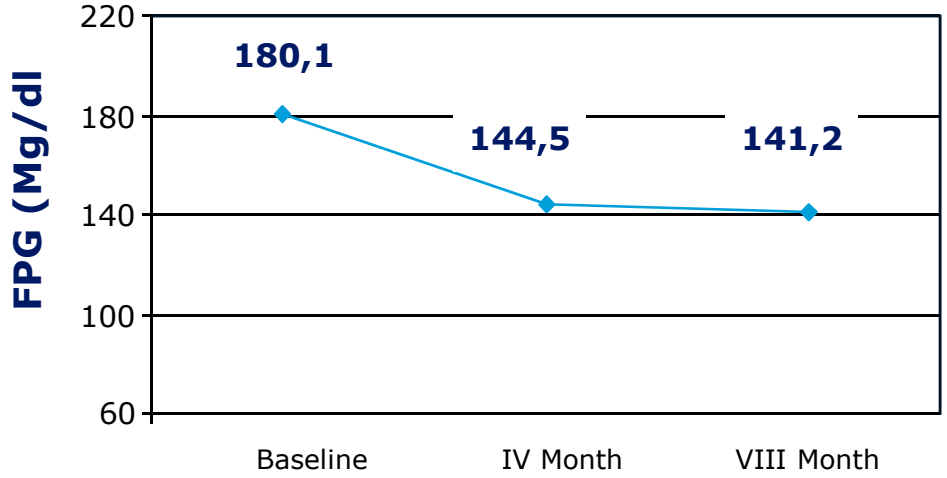


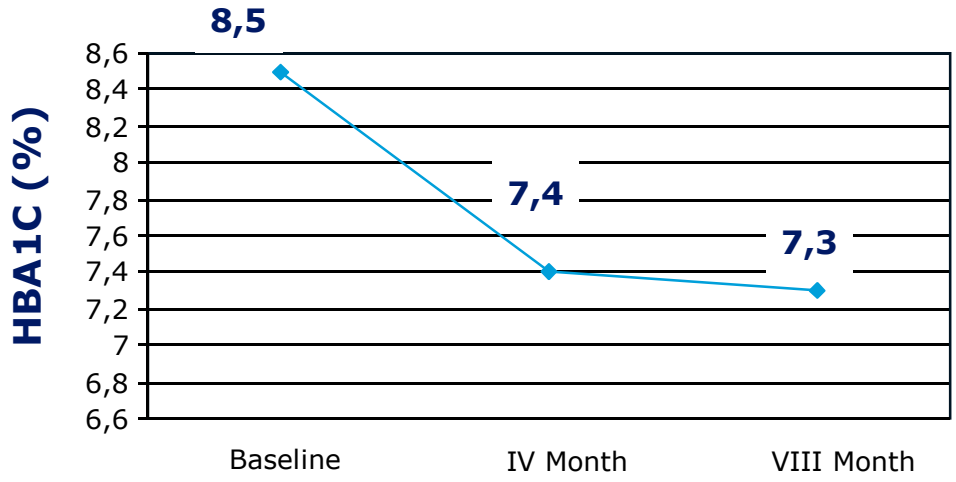
Liraglutide data: co-usage of other OADs after starting treatment

	N. pazienti
Gruppo terapeutico	
Biguanidi	22162
Sulfoniluree	7980
Glitazoni	2242
Glinidi	1610
Inibitori dell'Alfa-Glucosidasi	313

Baseline data after IV and VIII months

Total pts: 24273; pts at IV month: 11.508; pts at VIII month: 5181 (data are means)

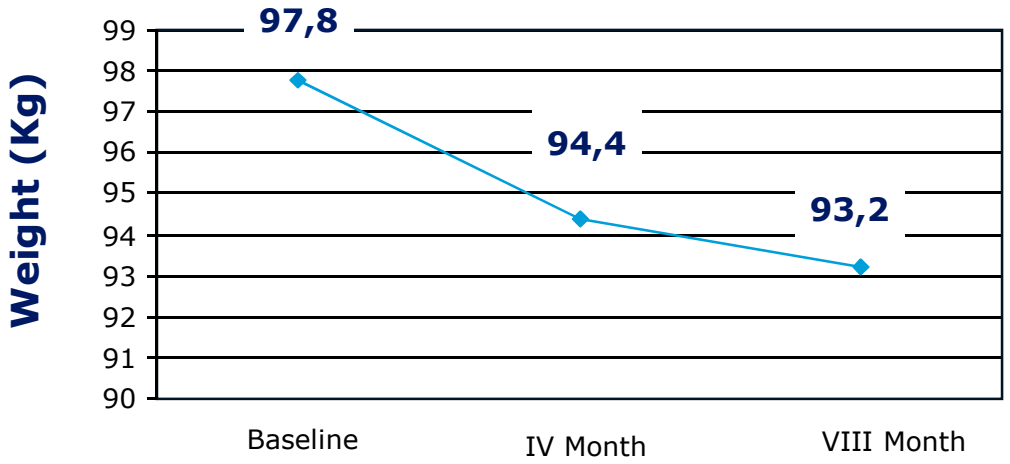


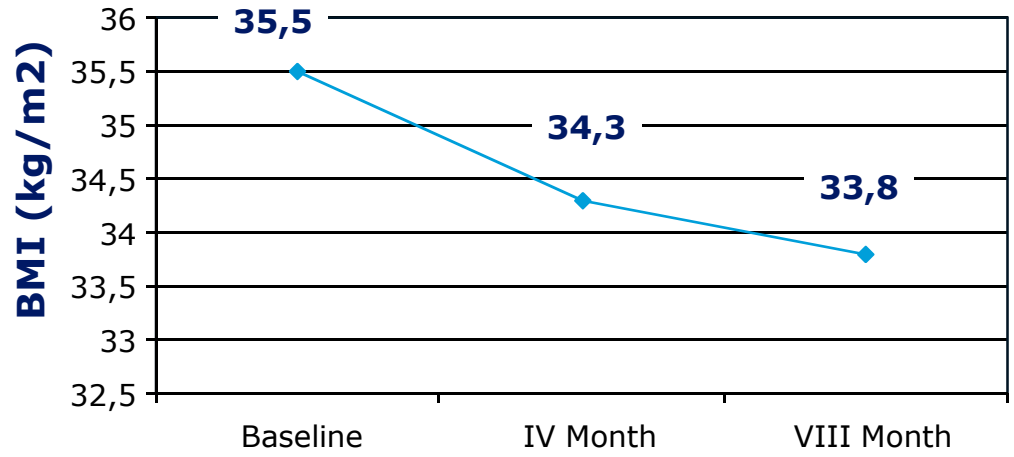


At 8 month, has achieved a reduction in HbA1c of -1.2%

Baseline data after IV and VIII months

Total pts: 24273; pts at IV month: 11.508; pts at VIII month: 5181 (data are means)



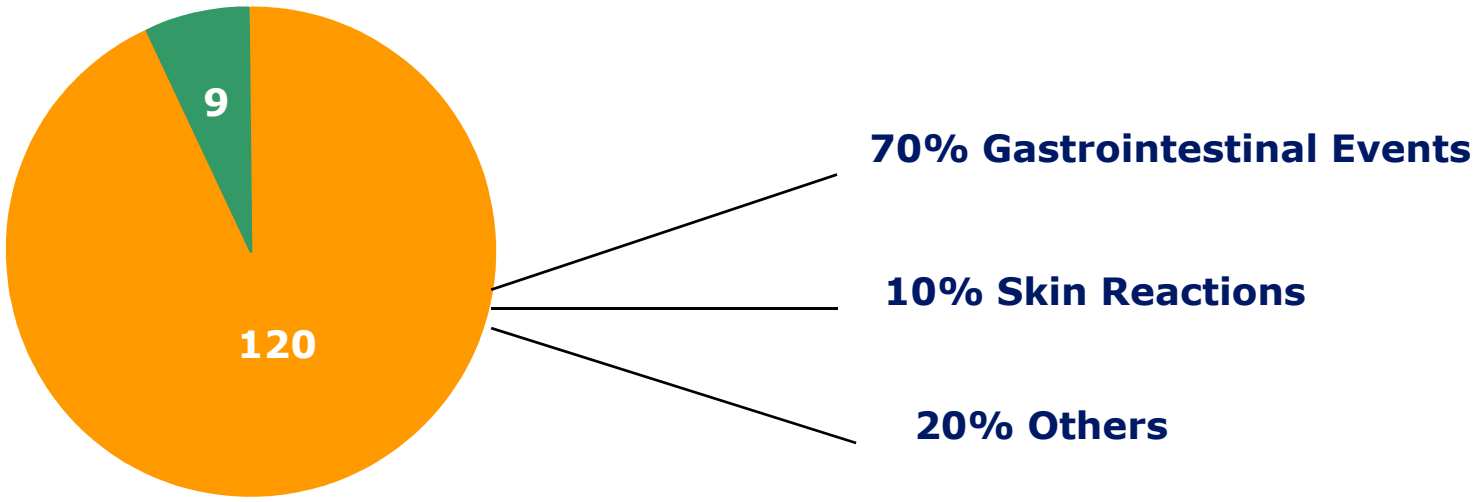


At 8 month, has achieved a reduction in weight of -4,6 kg, in BMI of -1,7 kg/m^2 and in WC of -3,7cm.

Suspected adverse reactions

(N° of episodes; total pts: 24140)

Gravità	N. ADR	%
Not serious	120	93.0
Serious	9	7.0
Totale	**129**	**100.0**



Summary

- Patients who started treatment with Liraglutide were with mean age 59, starting with HbA1c of 8,6 and very overweight (114,8 kg and 34,5 of BMI).
- 64,6% of them had already been treated with metformin (in monotherapy or in association with SUs or TZDs).
- At final follow up, the reduction in HbA1c is 1.2% and body weight is reduced by -4,6 kg, confirming and in some cases giving even better results respect data obtained in the LEAD program
- the most common adverse reactions non-serious were gastrointestinal events (nausea, vomiting, diarrhea) occurred in 70% of patients

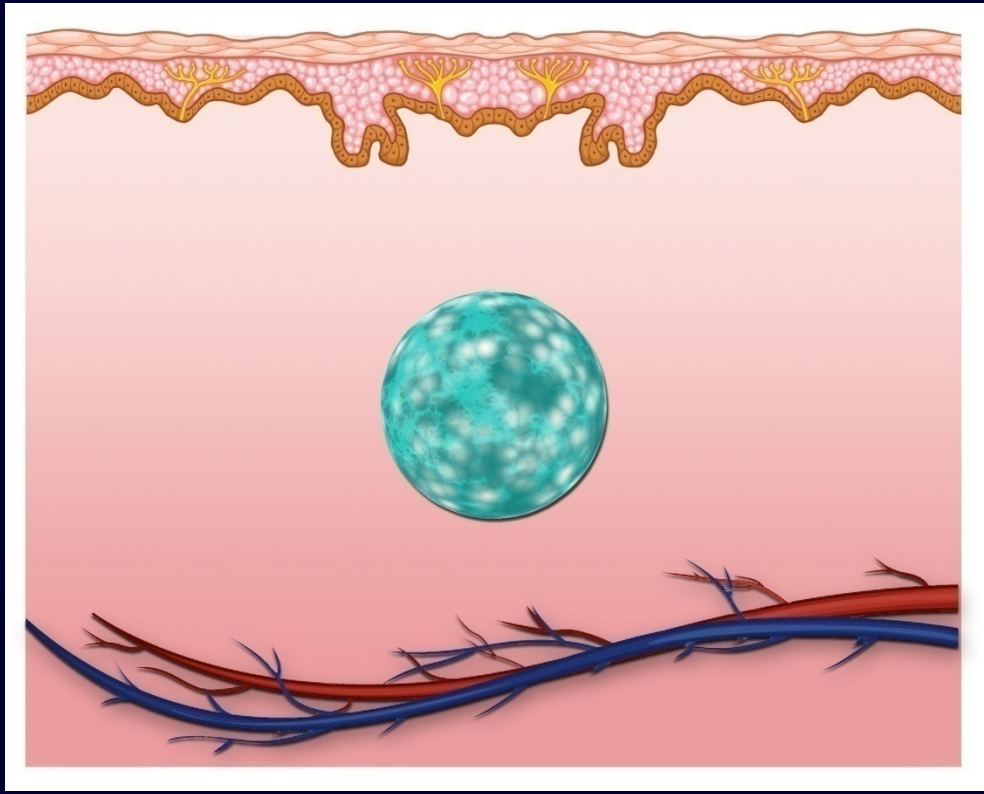
Development of Exenatide QW

- Exenatide is incorporated into polylactide co-glycolide (PLG) microspheres[1]
- PLG is a common medical biodegradable polymer (degraded to CO_2 and water) used in medical sutures and extended-release pharmaceuticals that allows gradual drug delivery at a controlled rate[2]
- EQW was developed using microsphere drug delivery technology to improve:
  - Fasting and postprandial glycaemic control
  - Convenience and adherence via a reduced number of subcutaneous (SC) injections
  - Tolerability (due to the gradual accumulation of exenatide to steady-state plasma concentrations)

1. Malone J, et al. *Expert Opin Investig Drugs.* 2009;18:359-367. 2. Tracy MA, et al. *Biomaterials.* 1999;20:1057-1062.

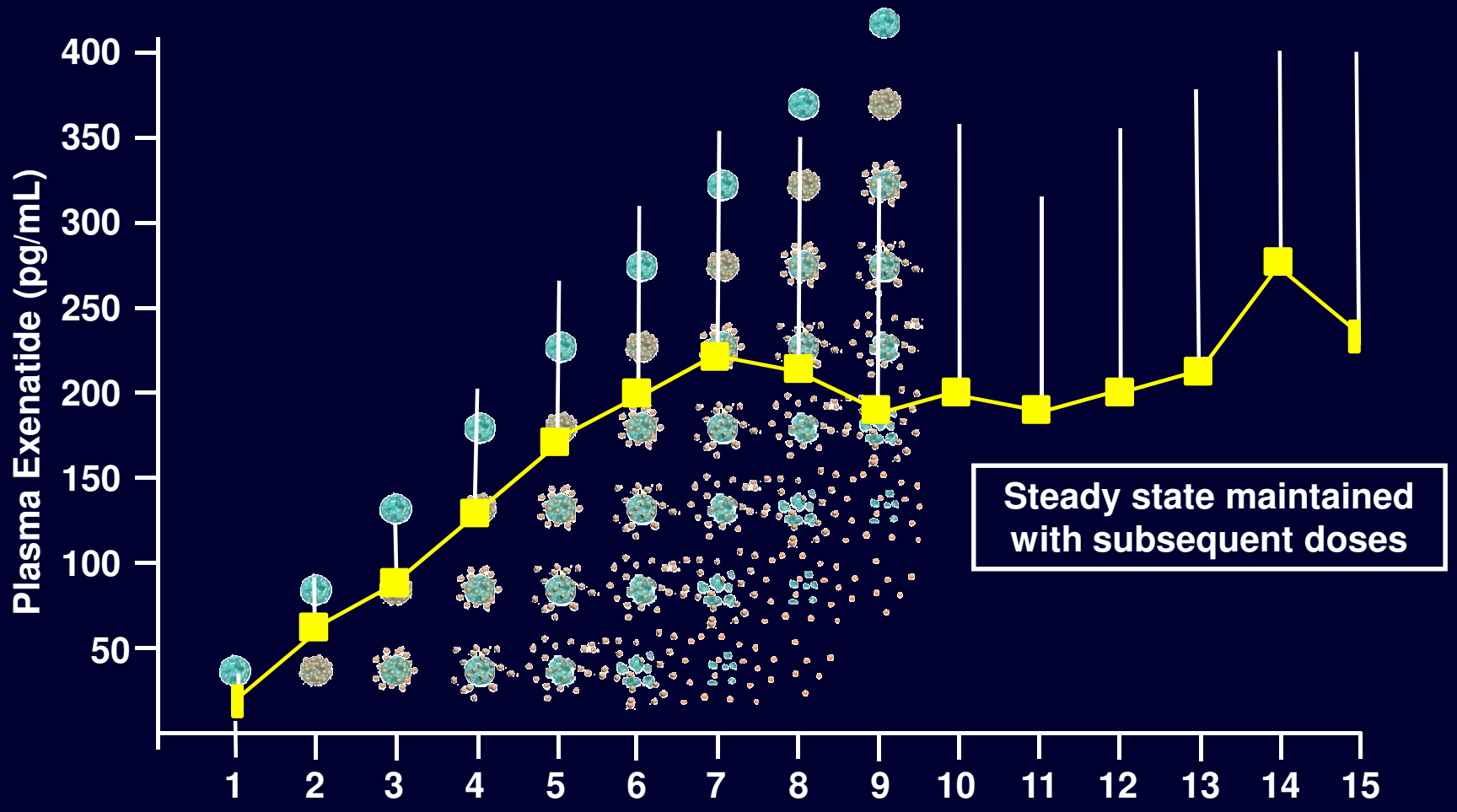
The Microsphere Delivery System Provides Continuous Therapeutic Levels of Exenatide

- Via hydration, exenatide at or near the surface dissolves and diffuses away (initial release)[1]
- PLG degrades, creating pores for exenatide diffusion and release from microspheres (sustained release)[1]
- It takes about 2 weeks to achieve concentrations in the therapeutic range[2]
- Steady-state exenatide concentration is reached at 6-7 weeks[3]



1. Bartus RT, et al. *Science*. 1998;281:1161-1162. 2. Kim D, et al. *Diabetes Care*. 2007;30:1487-1493. 3. Buse JB, et al. *Diabetes Care*. 2010;33:1255-1261.

EQW: Achieving Steady State (Schematic Representation)



Based on Kim D, et al. *Diabetes Care*. 2007;30:1487-1493.

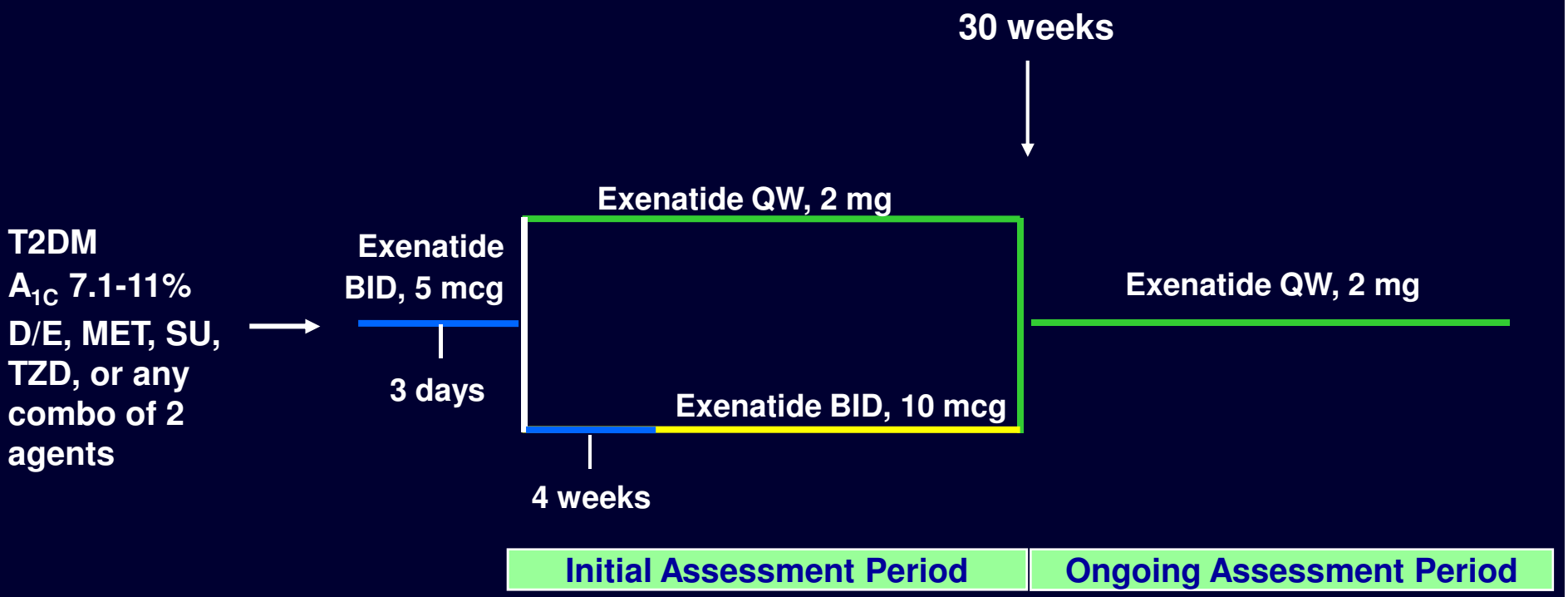
Overview of DURATION Trials

Study Name	Comparator	Population	Subjects	Duration
DURATION-1[1]	Exenatide BID Open label	Drug naïve or ≥1 oral antidiabetic agents	295 ITT	30 weeks plus open-ended OLE
DURATION-2[2]	Sitagliptin or pioglitazone Double blind	MET failures	491 ITT	26 weeks plus open-ended OLE
DURATION-3[3]	Insulin glargine Open label	MET ± SU failures	456 ITT	26 weeks plus 2.5-year OLE
DURATION-4[4]	MET, pioglitazone, or sitagliptin Double blind	Drug naïve	~800 enrolled	26 weeks plus 10-week safety follow-up
DURATION-5[5]	Exenatide BID Open label	Drug naïve or ≥1 oral antidiabetic agents	252 ITT	24 weeks
DURATION-6[6]	Liraglutide Open label	≥1 oral antidiabetic agents	~900 enrolled	26 weeks plus 10-week safety follow-up

- BID: twice a day, MET: metformin, SU: sulfonylurea, OLE: open-label extension, ITT: Intent-to-treat

1. Drucker et al. *Lancet* 2008;372(9645):1240-50.
2. Bergenstal et al. *Lancet* 2010;376(9739):431-39.
3. Diamant et al. *Lancet* 2010;375(9733):2234-43.
4. ClinicalTrials.gov (NCT00676338).
5. Blevins et al. *J Clin Endocrin Metab* 2011;96(5):2010-81.
6. ClinicalTrials.gov (NCT01029886).

DURATION-1 Study Design



*DURATION: (Diabetes Therapy Utilization : Researching Changes in A_{1C}, Weight and Other Factors Through Intervention with Exenatide ONce Weekly)

Drucker DJ, et al. *The Lancet*. 2008; 372:1240-1250

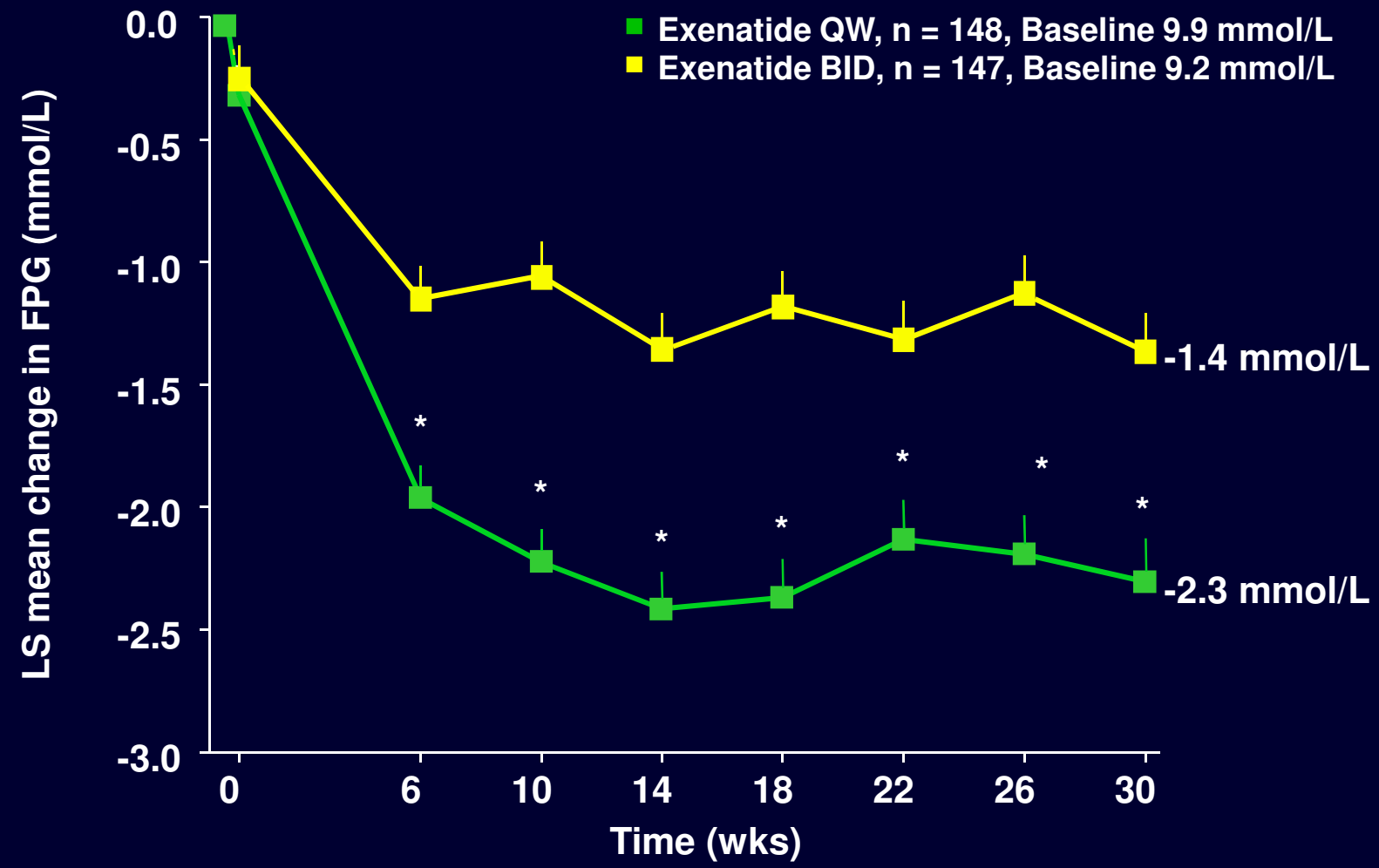
Patient Demographics and Baseline Characteristics (ITT, N = 295)

	Exenatide QW N = 148	Exenatide BID N = 147
Gender: Male/Female (%)	55 / 45	51 / 49
Age (y)	55 ± 10	55 ± 10
Body Weight (kg)	102 ± 19	102 ± 21
BMI (kg/m^2)	35 ± 5	35 ± 5
A_{1C} (%)	8.3 ± 1.0	8.3 ± 1.0
Fasting Plasma Glucose (mmol/L)	9.6 ± 2.4	9.2 ± 2.3
Race – White/Black/Asian/Hispanic (%)	83/6/0/11	73/13/1/14
Duration of Diabetes (y)	7 ± 6	6 ± 5

Data are n (%) or mean ± SD.

Drucker DJ, et al. *The Lancet*. 2008; 372:1240-1250

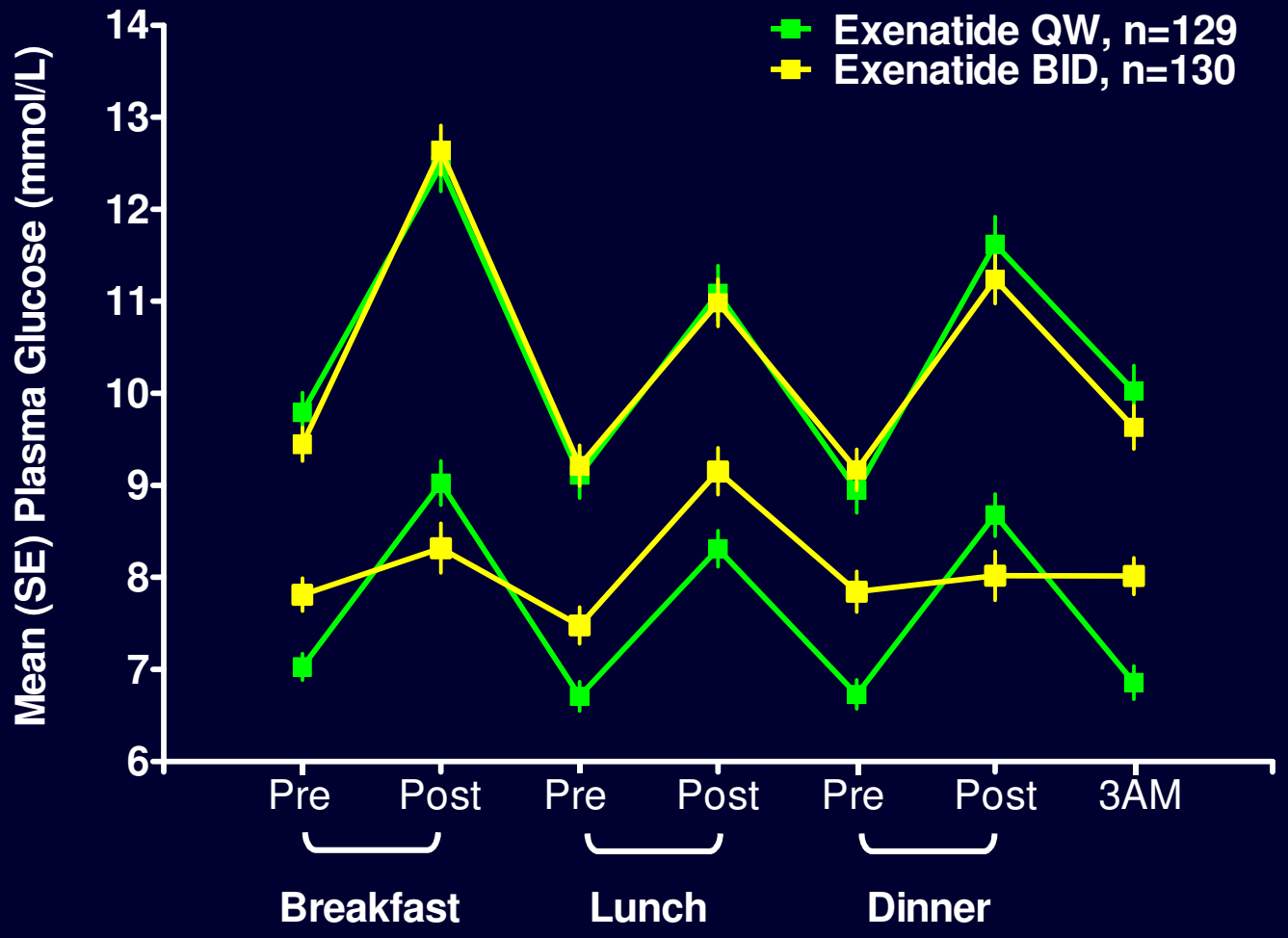
Change in Fasting Plasma Glucose From Baseline Over 30 Weeks



*p≤0.0001, QW vs. BID; ITT, N=295

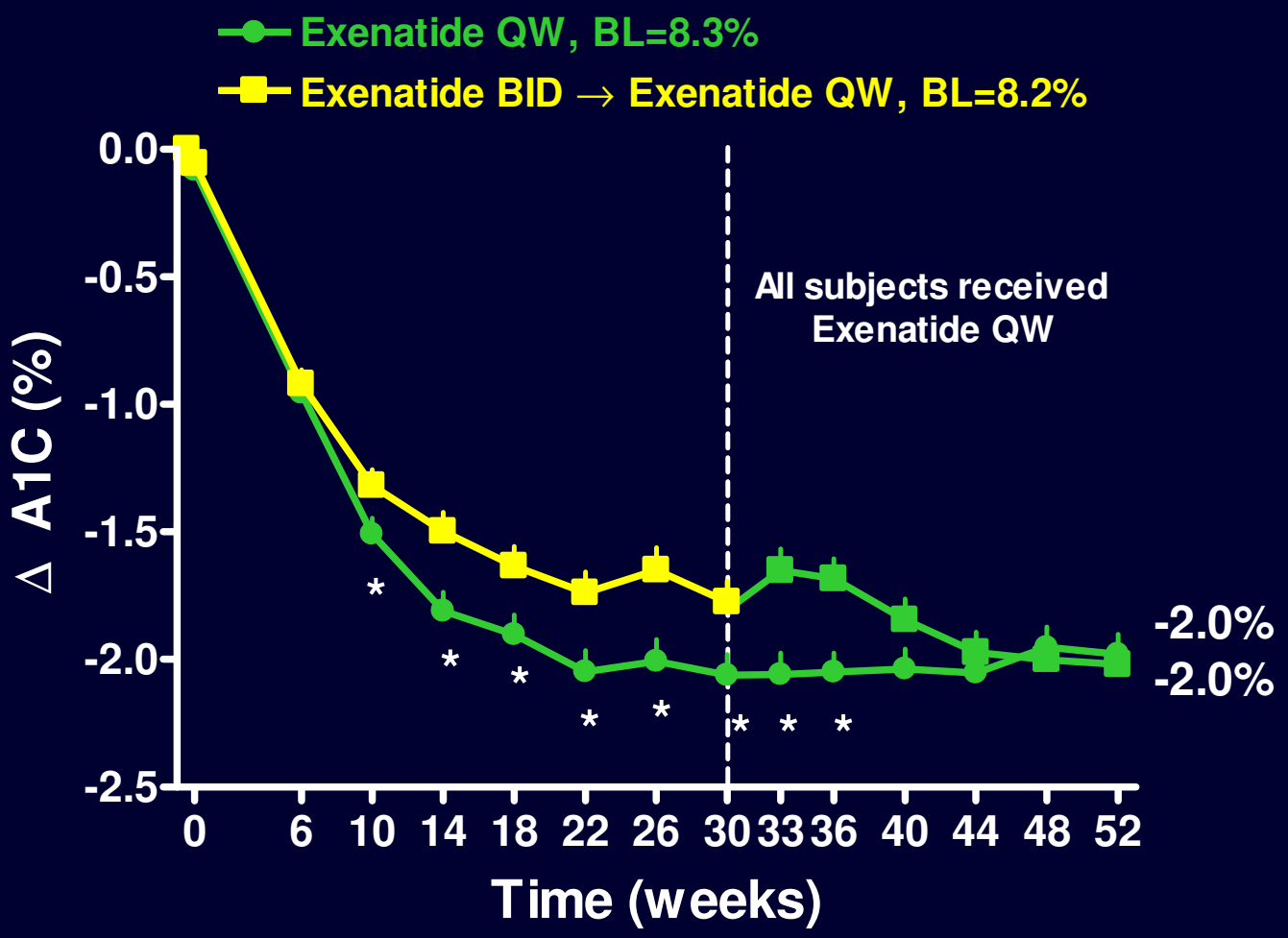
Drucker DJ, et al. *The Lancet*. 2008; 372:1240-1250

7-point Self-monitored Blood Glucose Profiles at Baseline and Week 30 (Evaluable, N = 259)



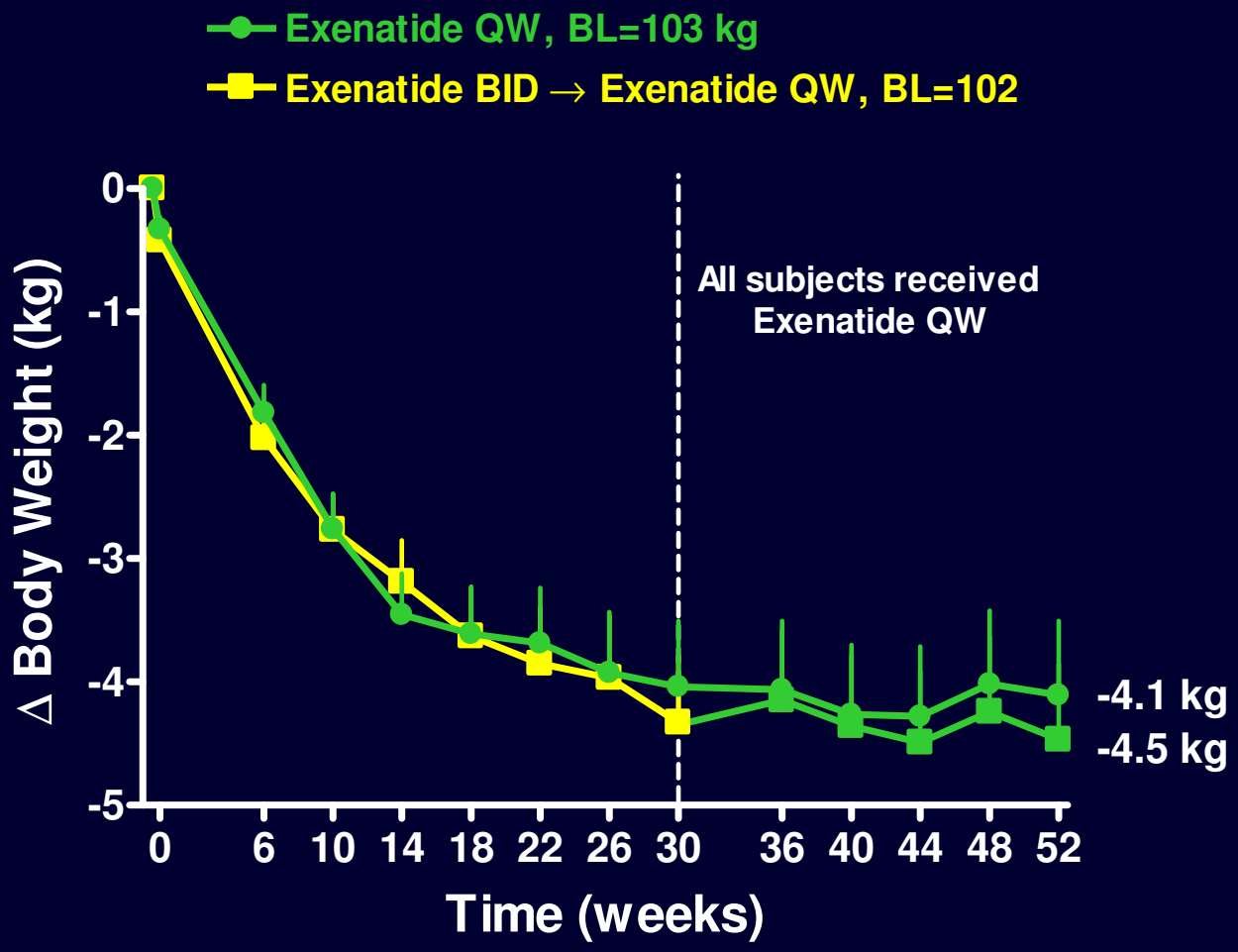
Drucker DJ, et al. *The Lancet*. 2008; 372:1240-1250

A1C Reduction Through Week 52



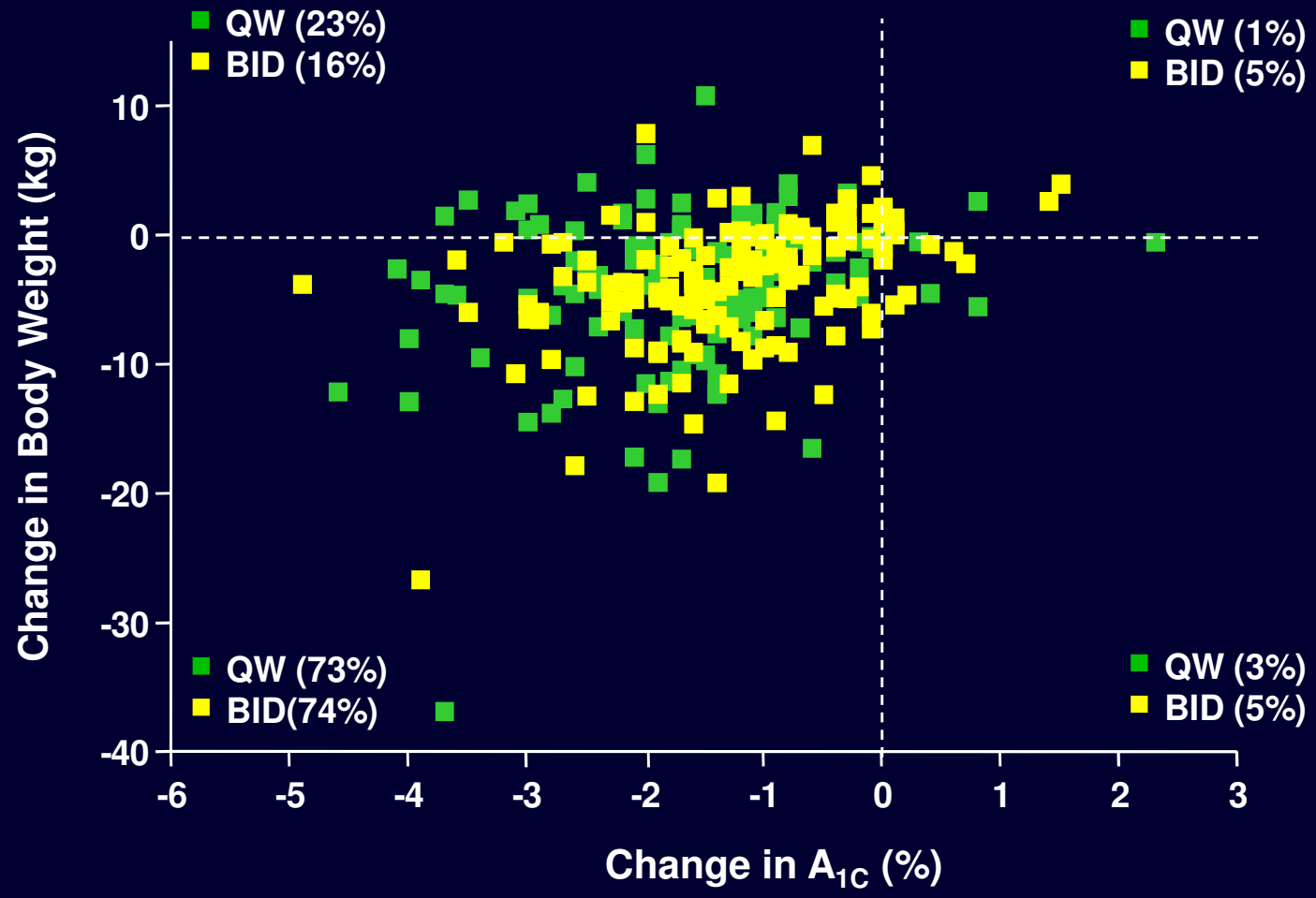
Data are LS mean ±SE; Evaluable (N=241); *p < 0.05, QW vs. BID

Body Weight Reduction Through Week 52



Data are LS mean ±SE; Evaluable (N=241); *p < 0.05, QW vs. BID

Individual Patient Data on Treatment Responses for A_{1C} and Body Weight



Drucker DJ, et al. *The Lancet*. 2008; 372:1240-1250

Overall Incidence of Treatment-emergent Adverse Events Occurring in 10% or More of Patients*

	Exenatide QW N = 148 %	Exenatide BID N = 145 %
Nausea	26.4	34.5
Vomiting	10.8	18.6
Injection site pruritus	17.6	1.4
Upper respiratory tract infection	8.1	17.2
Diarrhea	13.5	13.1
Constipation	10.8	6.2
Injection site bruising	4.7	10.3
Urinary tract infection	10.1	8.3

* Patients received 1 or more doses of study drug
Frequent treatment-emergent adverse events ≥10% incidence

Drucker DJ, et al. *The Lancet*. 2008; 372:1240-1250

Percentage of Patients With Hypoglycemia*, by Treatment and Concomitant Sulfonylurea Use

Hypoglycemia	Non-sulfonylurea Background		Sulfonylurea Background	
	Exenatide QW N = 93	Exenatide BID N = 93	Exenatide QW N = 55	Exenatide BID N = 54
Major (%)	0	0	0	0
Minor (%)	0	1.1	14.5	15.4

Data are n (%).

*at least one episode

Drucker DJ, et al. *The Lancet*. 2008; 372:1240-1250

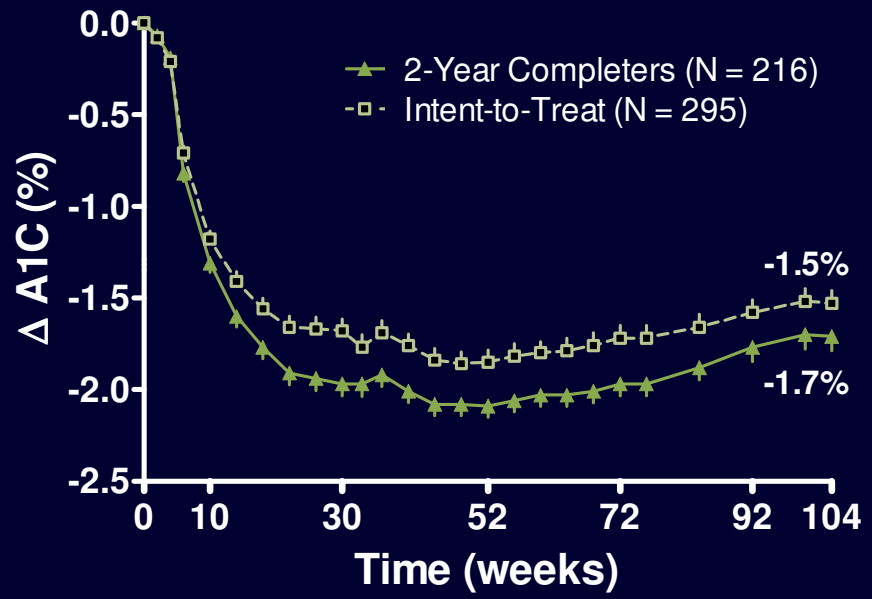
Overall Incidence of Treatment-Emergent Adverse Events Occurring in ≥5% of Patients

Adverse Event	Exenatide QW N = 128 %	Exenatide BID→QW N = 130 %
Upper respiratory tract infection	12.5	12.3
Diarrhea	8.6	6.9
Nausea	7.0	7.7
Nasopharyngitis	7.8	4.6
Sinusitis	4.7	6.9
Vomiting	6.3	4.6
Urinary tract infection	2.3	5.4
Injection site bruising	0	5.4

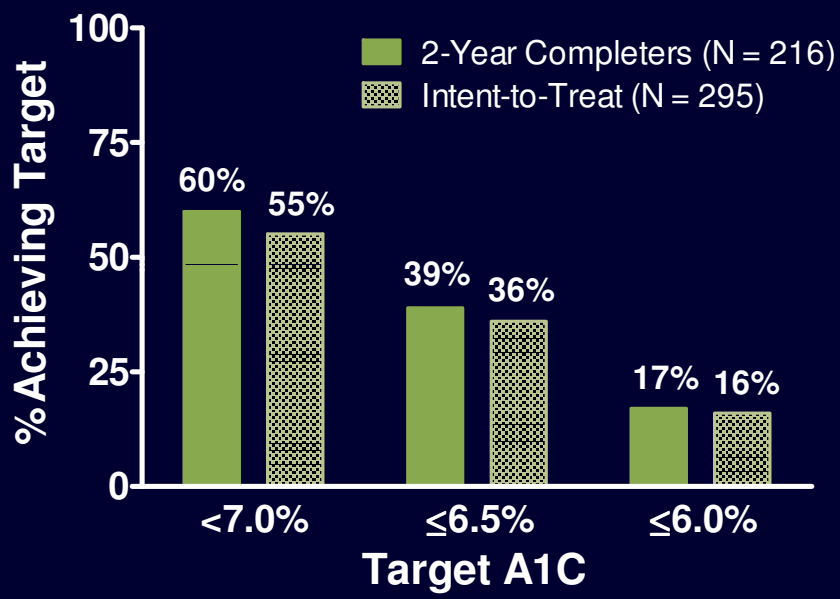
Open-ended assessment period ITT (N=258). Adverse events that occurred for the first time or existed before week 30 and worsened after the first injection at week 30 through study termination are reported.

Glycemic Control Improved Over 104 Weeks

A1C Change (%)

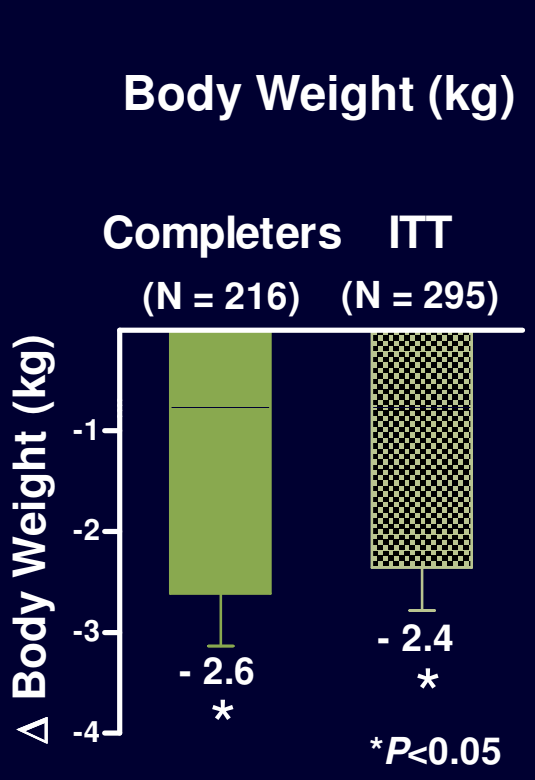


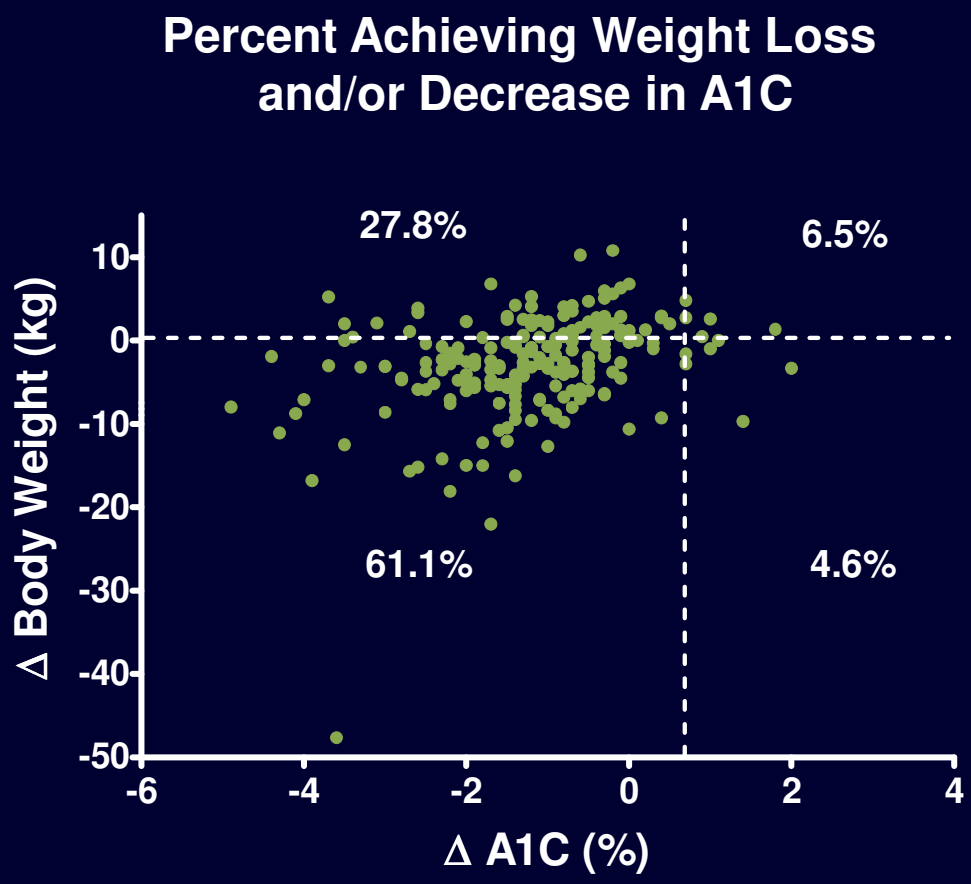
Percent Achieving Target A1C



Taylor, et al. *BMC Endocr Disord*. 2011;11(1):9.

Reductions in Body Weight and Weight + A1C Seen Through Week 104





Taylor, et al. *BMC Endocr Disord.* 2011;11(1):9.

Conclusions

- This study demonstrated sustained reductions in A1C and weight loss with long-term exenatide QW therapy
  - The once-weekly formulation of exenatide produced continuous GLP-1 receptor activation leading to sustained control of both fasting and postprandial hyperglycemia, which resulted in enhanced reductions in A1C
- Reductions in systolic blood pressure and lipids were also sustained
- Exenatide QW was well tolerated during the 2 years of treatment and common AEs, especially nausea, subsided with time
  - Few patients experienced hypoglycemia, and most of these patients were using a concomitant sulfonylurea

Taylor, et al. *BMC Endocr Disord*. 2011;11(1):9.

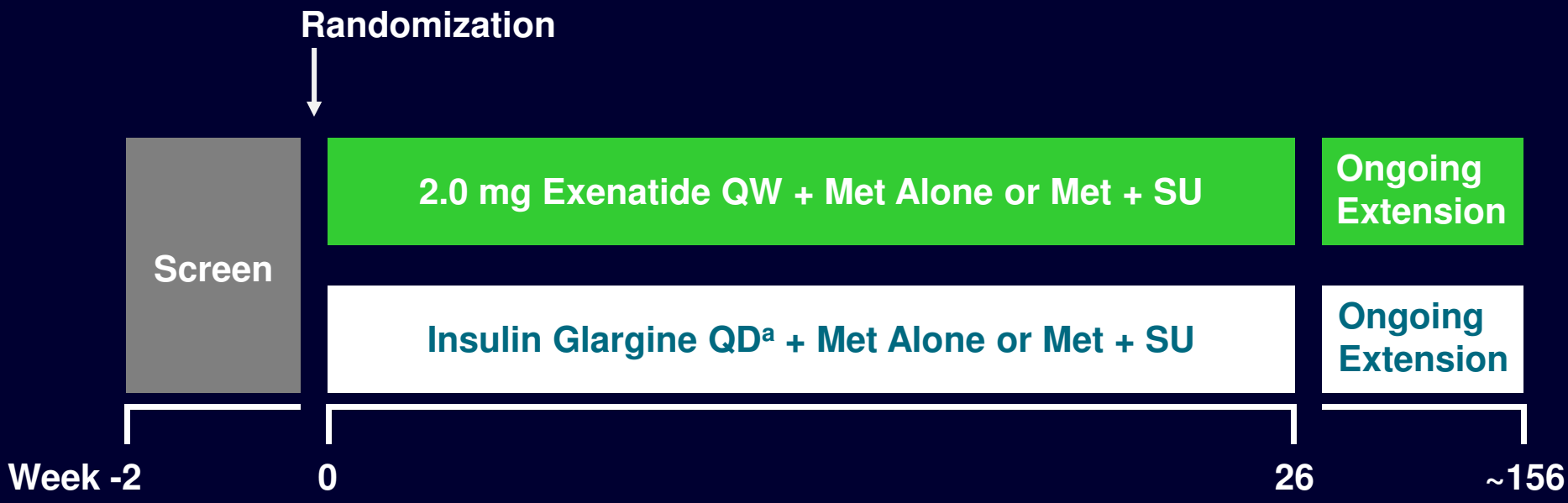
DURATION-2 Study Design

Inclusion criteria

- A1C ≥7.1% and ≤11.0%
- BMI ≥25 and ≤45 kg/m^2
- Stable body weight for ≥3 months
- Stable dose of Met ≥1500 mg for ≥8 weeks

Exclusion criteria

- 3+ episodes of major hypoglycemia within 6 months
- Treated with an excluded medication within 3 months



[a]Dosed to a fasting glucose target of 4.0 – 5.5 mmol/L

A1C = hemoglobin A1c; BMI = body mass index; Met = metformin; SU = sulfonylurea; QD = once daily; QW = once weekly

Diamant M, et al. *Lancet* 2010; 375: 2234-43.

Study Objectives

- Primary objective
  - Test the hypothesis that improvement in A1C achieved with exenatide QW is superior to insulin glargine titrated to target
- Secondary and exploratory objectives
  - Proportions of subjects achieving A1C targets (<7.0% and <6.5%)
  - Fasting serum glucose
  - Self-monitored blood glucose profiles
  - Body weight and waist/hip circumference
  - Fasting serum lipids and other cardiovascular markers
  - HOMA-B and HOMA-S
  - Health outcomes
  - Safety

QW = once weekly; A1C = hemoglobin A1c
HOMA-B = homeostasis model assessment of beta cell function; HOMA-S = homeostasis model assessment of insulin sensitivity

Diamant M, et al. *Lancet* 2010; 375: 2234-43.

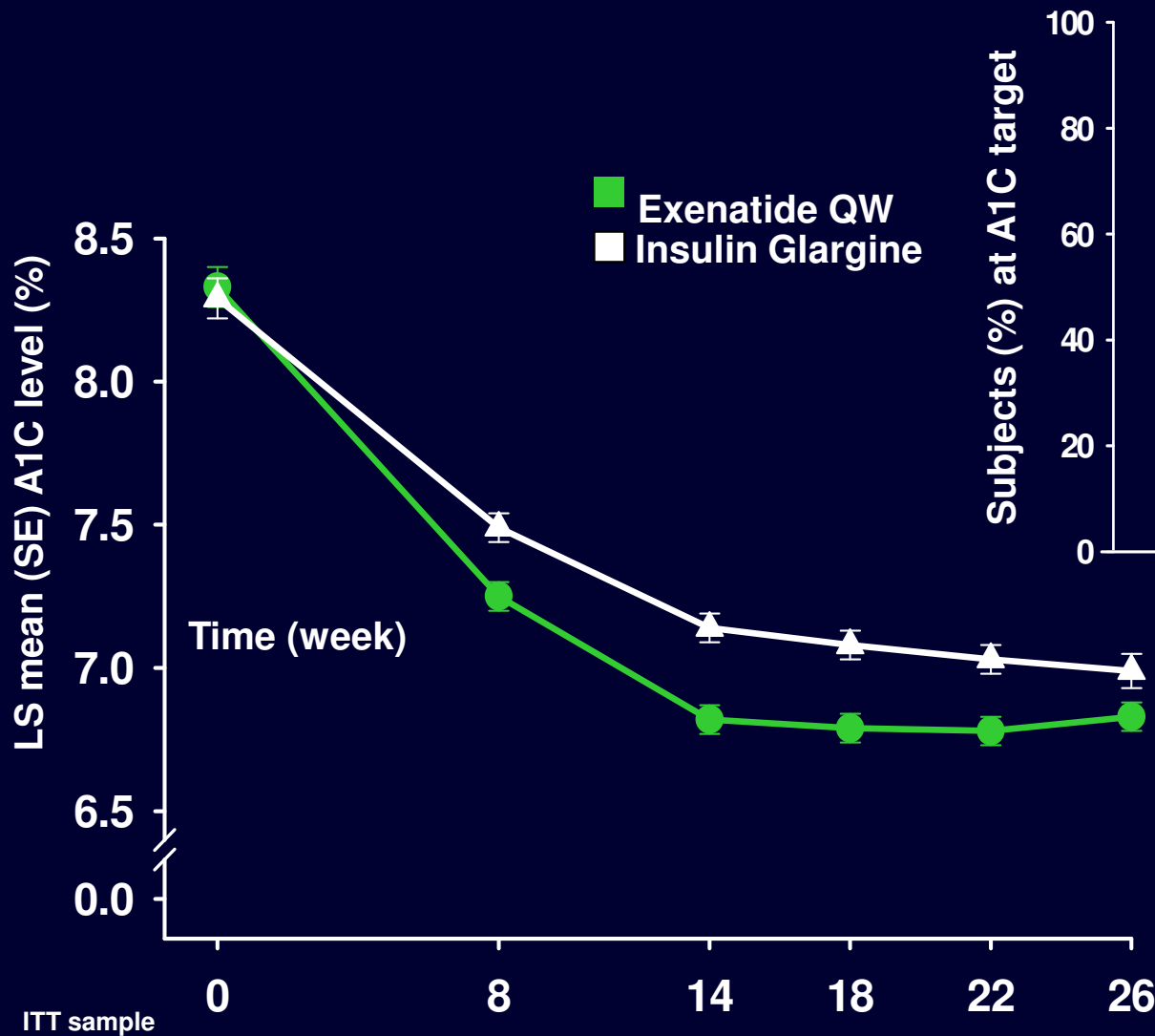
Subject Baseline Characteristics

	Exenatide QW (N=233)	Insulin Glargine (N=223)
Age, years	58 ± 10	58 ± 9
Gender, female, n (%)	113 (48)	100 (45)
Race, n (%)		
African American	2 (1)	1 (<1)
Caucasian	190 (82)	189 (85)
Asian	13 (6)	14 (6)
Hispanic	28 (12)	19 (8)
Weight, kg	91.2 ± 18.6	90.6 ± 16.4
BMI, kg/m^2	32 ± 5	32 ± 5
A1C, %	8.3 ± 1.1	8.3 ± 1.0
FSG, mmol/L	9.9 ± 2.5	9.7 ± 2.7
Duration of diabetes, years	8.0 ± 6.0	7.8 ± 6.0
Patients on Met alone, n (%)	164 (70)	157 (70)

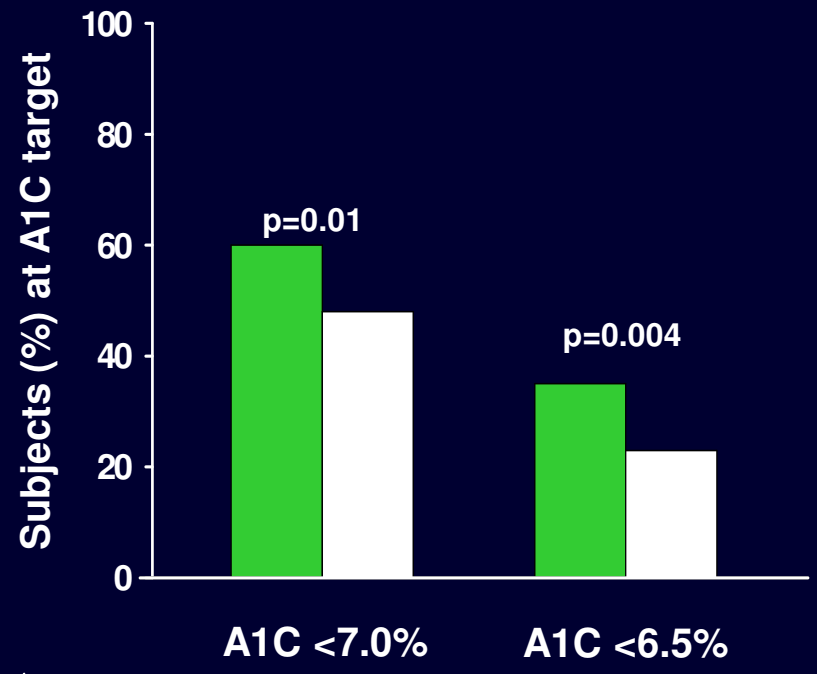
A1C = hemoglobin A1c; BMI = body mass index; FSG = fasting serum glucose; Met = metformin; QW = once weekly

Diamant M, et al. *Lancet* 2010; 375: 2234-43.

Primary Endpoint: Change in A1C



Achievement of A1C targets

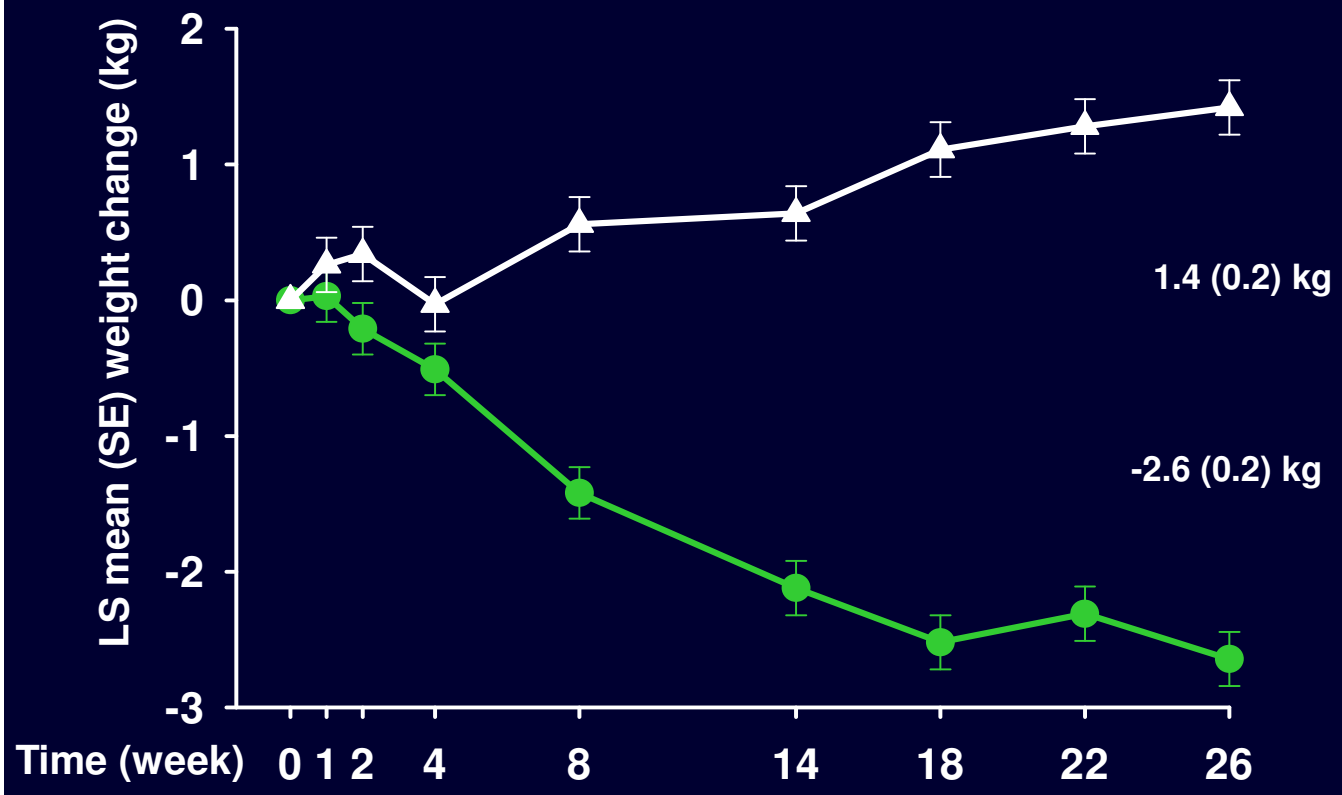


ITT sample

*Significant between-group difference, p<0.05; A1C = hemoglobin A1c; LS = least squares; QW = once weekly; SE = standard error

Diamant M, et al. *Lancet* 2010; 375: 2234-43.

Changes in Body Weight



ITT sample; LS = least squares; ITT = intent to treat; QW = once weekly; SE = standard error
*Significant between-group difference, $p<0.05$
Mean body weight at baseline: exenatide QW, 91.2 (SE 1.2); insulin glargine 90.6 (1.2) kg
Diamant M, et al. *Lancet* 2010; 375: 2234-43.

Key Summary Findings

- Exenatide QW resulted in superior A1C reduction after 26 weeks
- Fasting glucose reduction was greater with insulin glargine, while exenatide QW improved postprandial glucose control
- Most exenatide QW subjects had reduced A1C and weight, while insulin-treated subjects had decreased A1C and weight gain
- Blood pressure and lipids were improved in both groups
- More subjects in the exenatide QW group discontinued due to adverse events
- Gastrointestinal adverse events were experienced more frequently by subjects in the exenatide QW group
- Hypoglycemia incidence was lower with exenatide QW

QW = once weekly; A1C = hemoglobin A1c

Diamant M, et al. *Lancet* 2010; 375: 2234-43.

Real-life prevalence of pancreatitis during treatment with exenatide or sitagliptin

Cases of acute pancreatitis in all patients initiated on exenatide (n=27.996) or sitagliptin (n=16.297) registered in a large commercial insurance database (Ingenix, United Health, US) in the years 2005-2008.

The exenatide and sitagliptin cohorts are compared to two matched cohorts of patients in the same database treated with metformin or glyburide (glibenclamide).

Absolute and relative risk of hospitalisation associated with a primary diagnosis of acute pancreatitis among exenatide or sitagliptin initiators compared with metformin or glyburide initiators by propensity score-matched drug pair, Ingenix Research Datamart, 6/1/2005-6/30/2008

	No. of cases	No. of patients	Absolute risk (%)	Relative risk	95% CI
Drug pair 1					
- Exenatide	37	27,996	0.13	1.0	0.6–1.7
- Metformin/glyburide	36	27,983	0.13	1.0	Ref
Drug pair 2					
- Sitagliptin	19	16,267	0.12	1.0	0.5–2.0
- Metformin/glyburide	19	16,281	0.12	1.0	Ref

CI, confidence interval

Dore DD, Ingenix database United Health; Current Medical Research and Opinions 2009; 25: 1019-1027

No increased risk of acute pancreatitis in patients with T2D treated with exenatide or sitagliptin

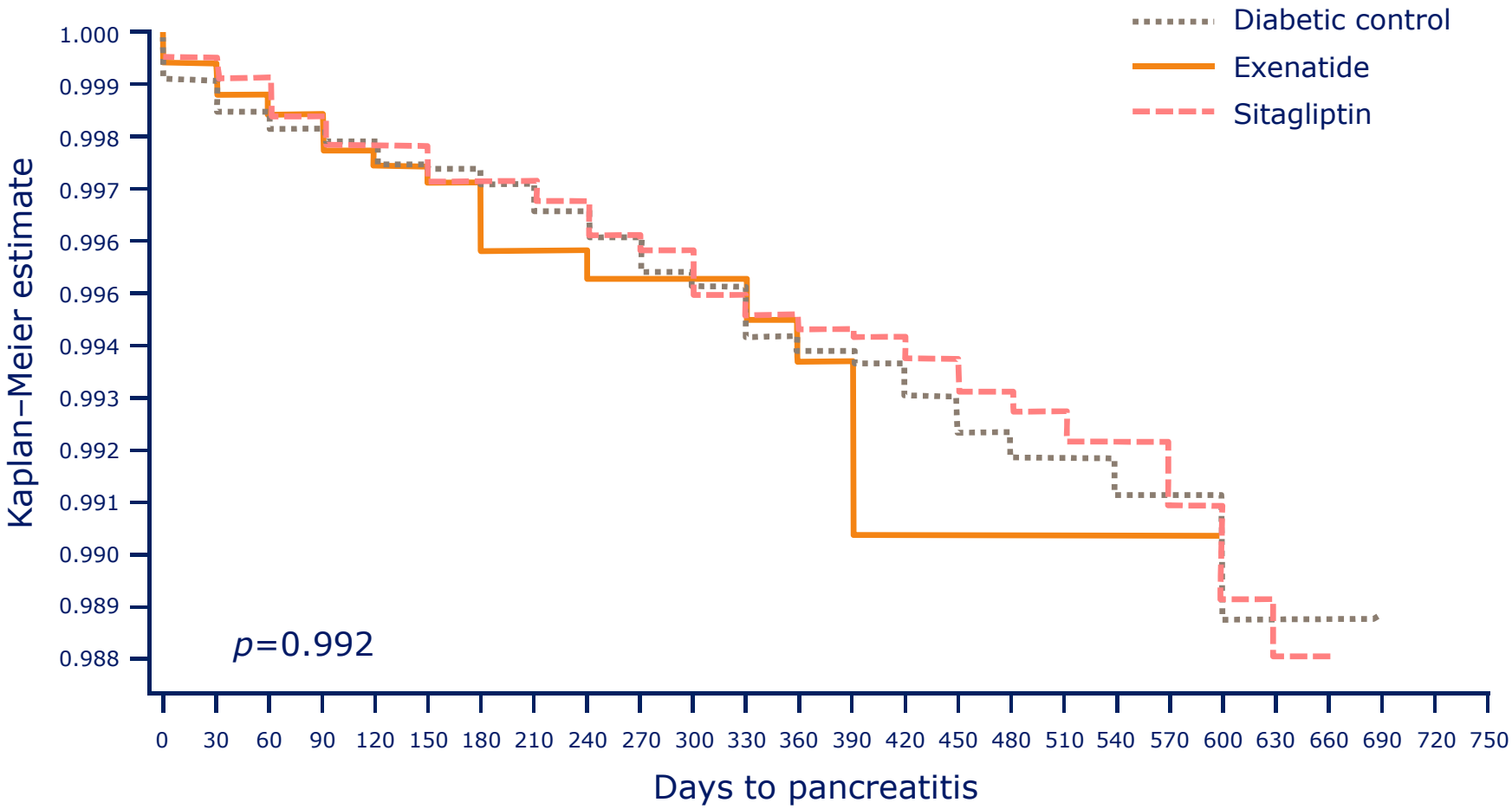
Pancreatitis	Non-diabetic	Diabetic	Exenatide	Sitagliptin	Diabetes control
Patient follow-up (years)	1.2 ± 0.4***	0.7 ± 0.5	0.6 ± 0.5###	0.8 ± 0.5†††	0.7 ± 0.5
New acute pancreatitis	1746 (0.2)***	154 (0.4)	22 (0.3)	67 (0.4)	65 (0.4)
Incidence of new acute pancreatitis (cases/100,000 patient*years)	190.5	563.9	569.9	554.4	571.9

Data are mean ± SD or n (%).
***$p<0.0001$ *vs.* diabetes; ###$p<0.0001$ *vs.* diabetes control; †††$p<0.0001$ *vs.* diabetes control

786,656 patients were analyzed retrospectively from a medical claims database

Garg *et al. Diabetes Care* 2010;33:2349-2354

No increased risk of acute pancreatitis with exenatide or sitagliptin

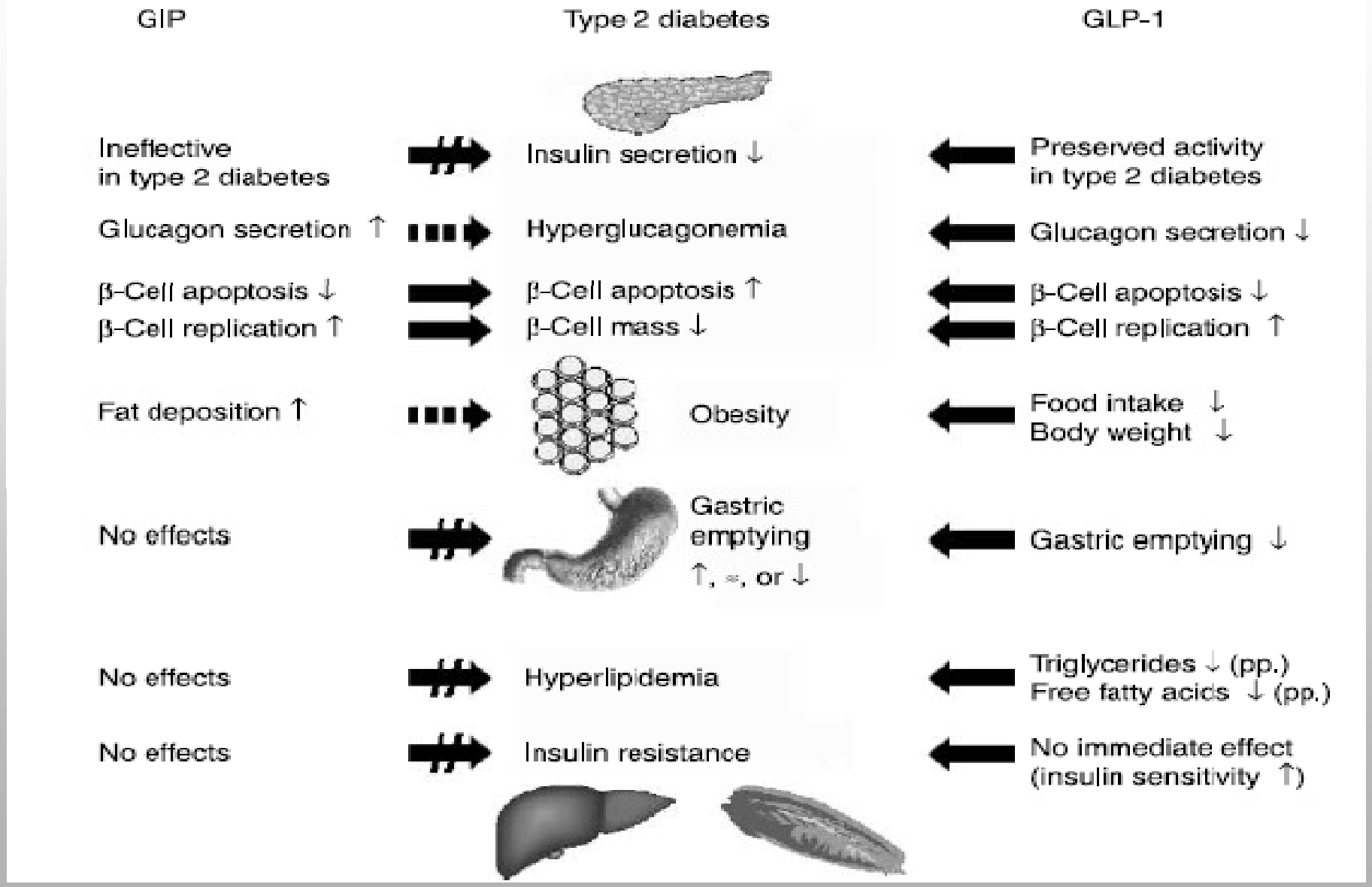


Garg *et al. Diabetes Care* 2010;33:2349-2354

Published cases of pancreatitis in liraglutide development program

- LEAD 1 (1 **chronic** case), published in Diabetic Medicine
  - A patient treated with **liraglutide 0.6mg**, occurred after 157 days and continued on liraglutide throughout the trial
- LEAD 2 (2 cases), published in Diabetes Care
  - A patient treated with **liraglutide 1.2mg**, occurred after 50 days and discontinued treatment.
  - A patient treated with **glimepiride**, occurred after 63 days and discontinued treatment.
- LEAD 3 (2 cases), published in Lancet
  - A patient treated with **liraglutide 1.2mg**; occurred after 197 days of treatment. Continued on liraglutide without re-occurrence of pancreatitis.
  - A patient treated with **liraglutide 1.8mg**; occurred after 313 days, discontinued treatment.
- LEAD 6 (1 **chronic** case), published in Lancet
  - 1 patient treated with **liraglutide 1,8mg**, occurred after 88 days and the patient continued on liraglutide throughout the trial
- Previous history of pancreatitis
  - Of patients recruited for the LEAD programme, 25 patients had previously had acute (17) or chronic (7) pancreatitis. None of these developed pancreatitis again during the treatment with liraglutide (data on file).

GIP+GLP-1 BASED THERAPIES?



IL-6 stimulates GLP-1 secretion in human islets and alpha cells