FOCUS SUI NUOVI FARMACI:

"GLP1-R agonisti long acting"

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Il dr. ***Riccardo Candido*** dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

Novartis

Roche Diagnostics

Johnson & Johnson Medical

Eli Lilly Italy

Astra Zeneca-Bristol Myers Squibb

Merck Sharp & Dohme

Chiesi Farmaceutici

Sigma-Tau

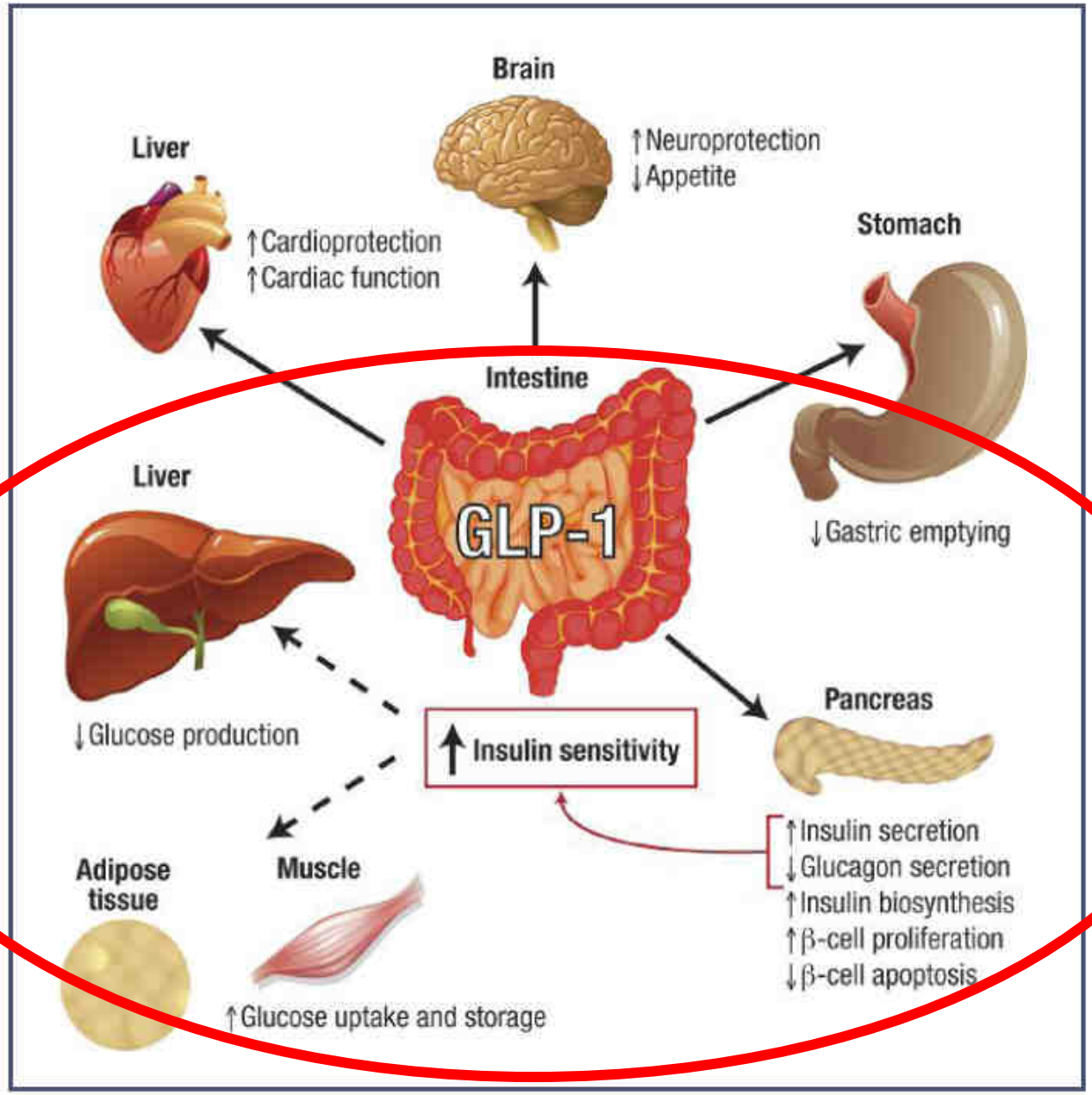
Novartis

ForFarma

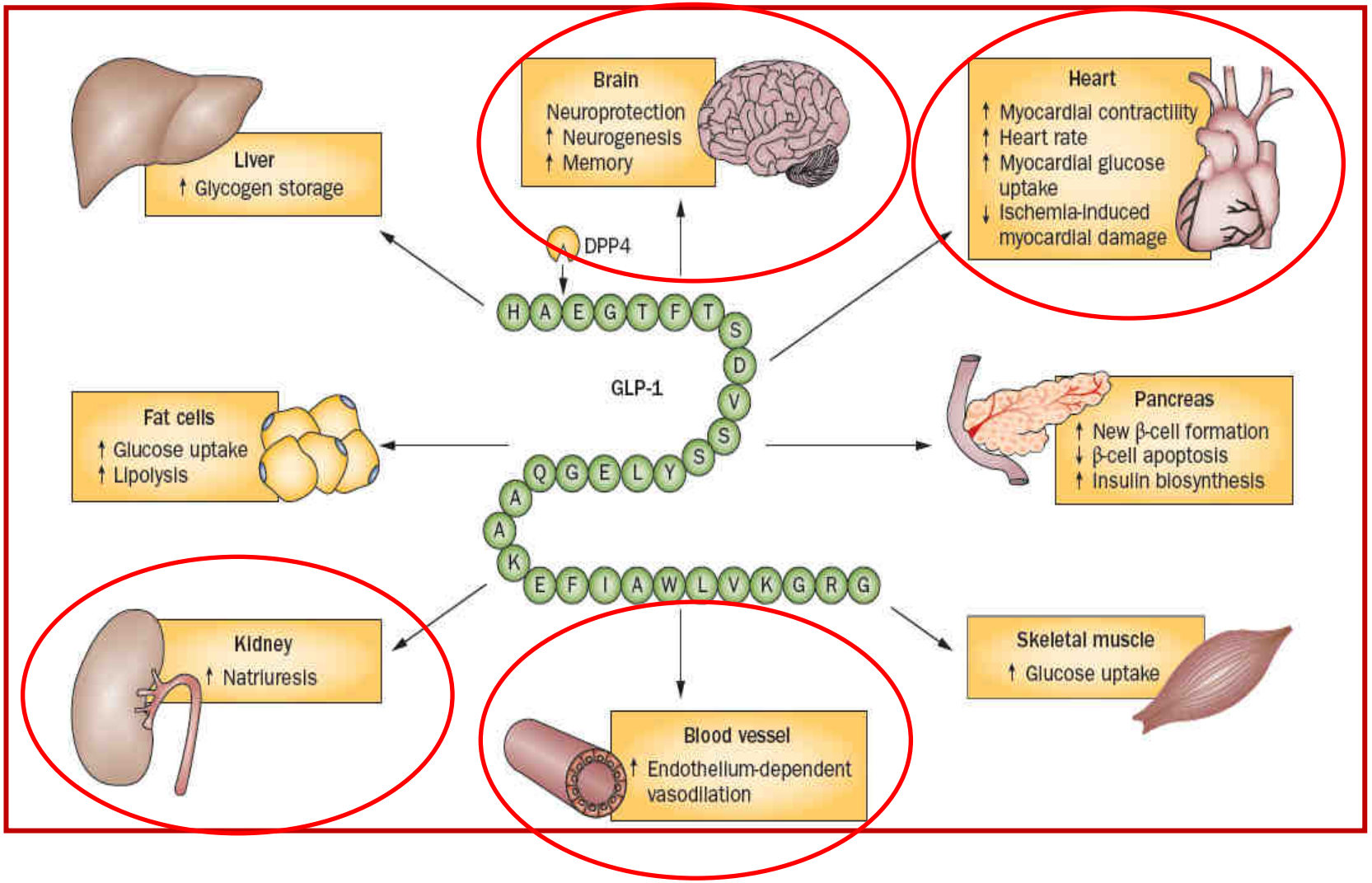
Novo Nordisk

Rottapharm

Multiple physiologic effects of GLP-1



Pleiotropic effects of GLP-1 or GLP-1 receptor agonists



Meier JJ, *Nat. Rev. Endocrinol. 8, 728–742 (2012)*

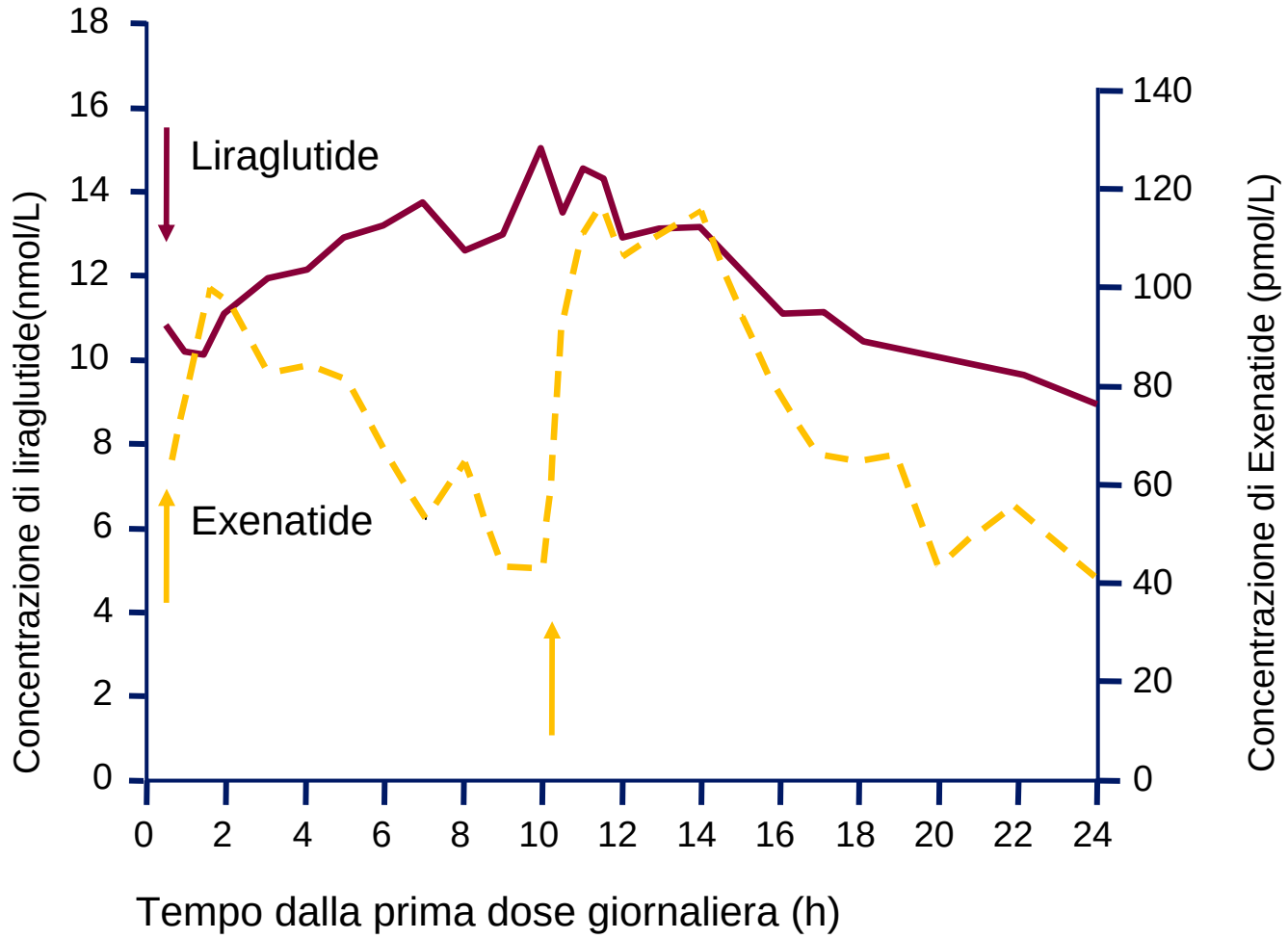
Long-Acting Glucagon-Like Peptide 1 Receptor Agonists

A review of their efficacy and tolerability

Short-acting <24 h	Long-acting ≥24 h	
Twice daily	Once daily	Once weekly
Exenatide (launched)	Liraglutide (launched)	Exenatide LAR (phase 3) Taspoglutide (phase 3) Albiglutide (phase 3) LY2189265 (phase 2)

Garber AJ, Diabetes Care 2011, 34 (suppl 2): S279-S284

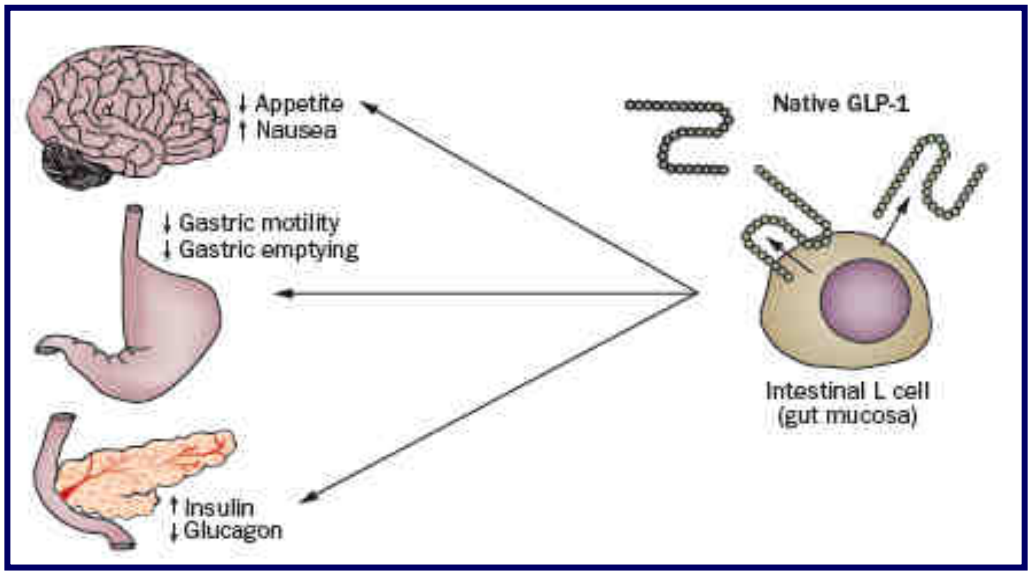
Confronto liraglutide vs exenatide: steady-state dei livelli plasmatici nelle 24 h

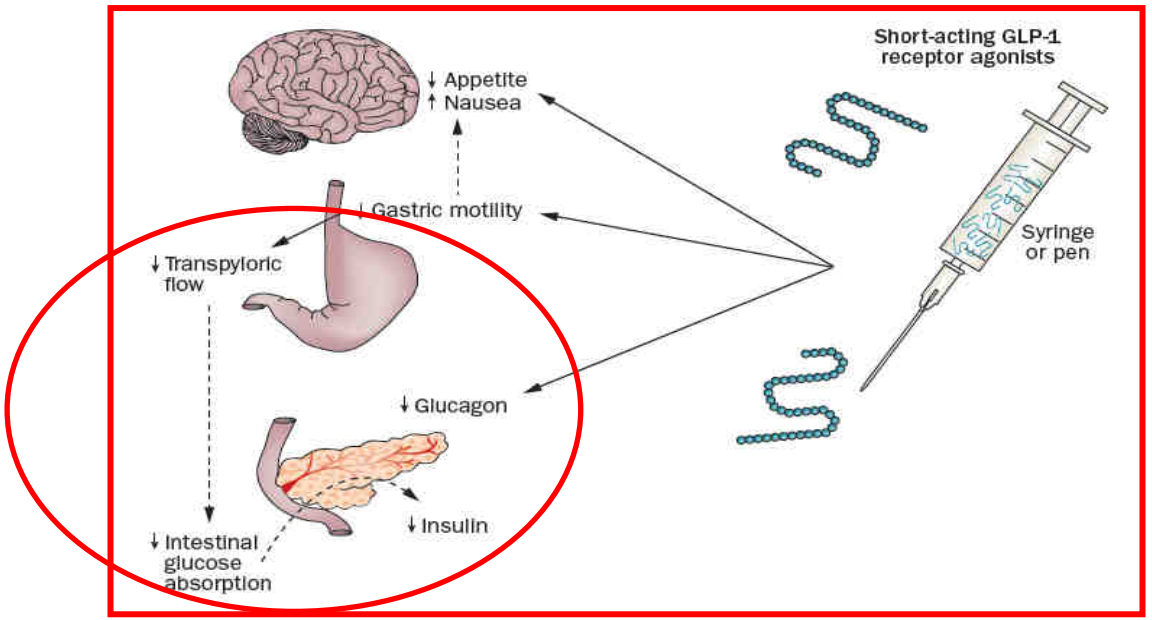


Exenatide è stato somministrato al mattino (timepoint 0 h) e alla sera (timepoint 10 h)(evidenziato dalle frecce).

Rosenstock *et al*. Diabetes 2009; 58 (Suppl 1):558-P

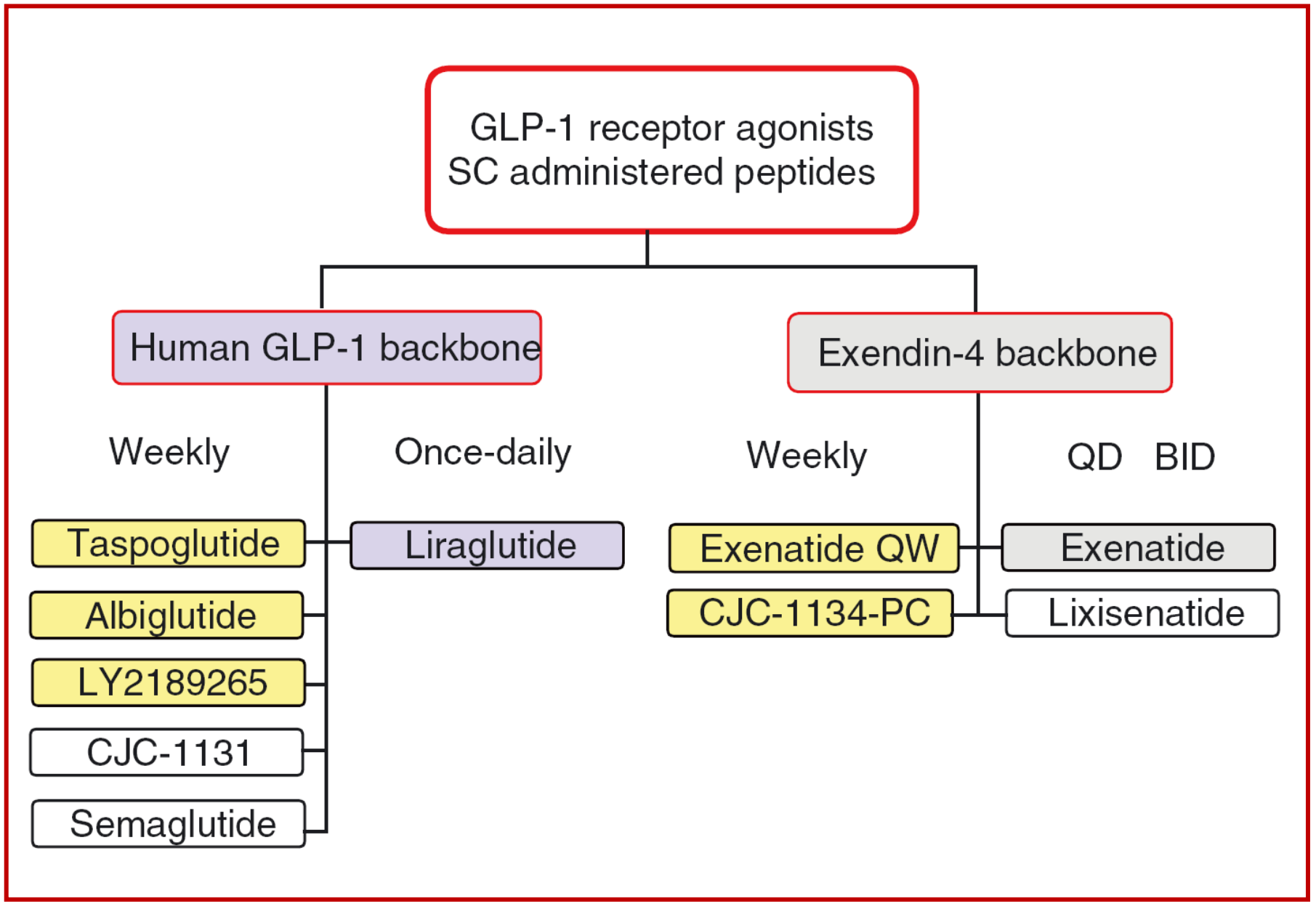
Physiological role of GLP-1 and short acting GLP-1 receptor



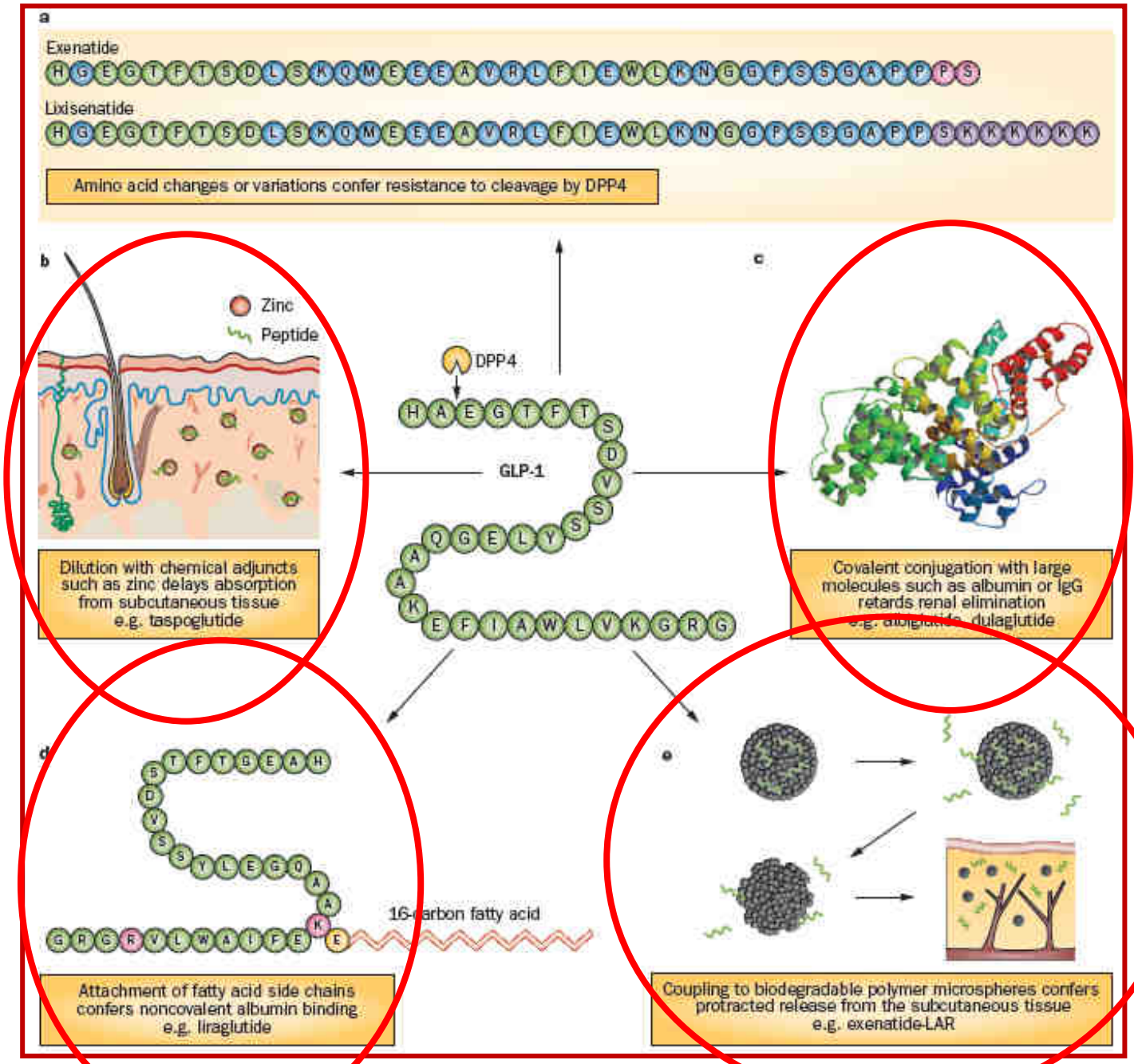


Limiti dei GLP-1 short-acting

- **Efficacia (riduzione HbA1c)**
- **Modesto effetto sulla glicemia a digiuno**
- **Variabilità glicemica**
- **Frequenti somministrazioni**
- **Effetti collaterali (nausea, vomito, diarrea)**

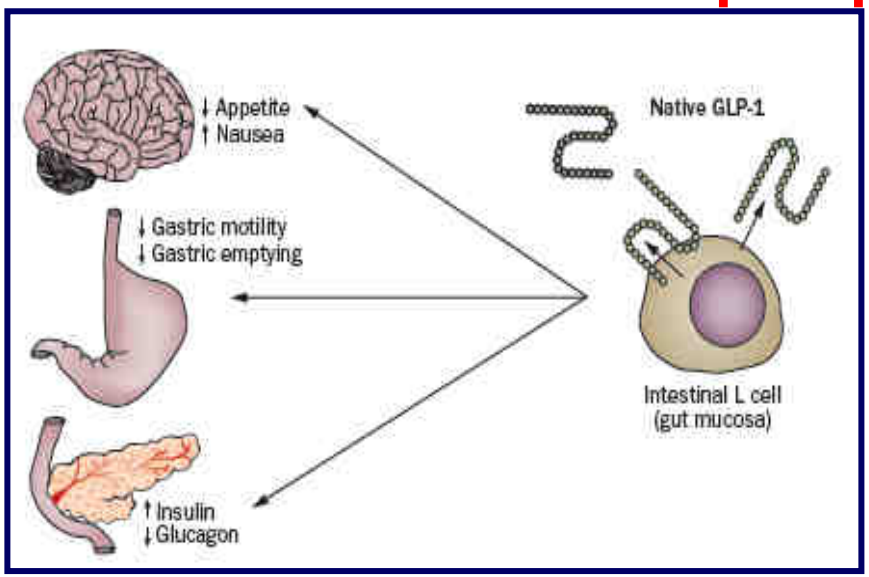


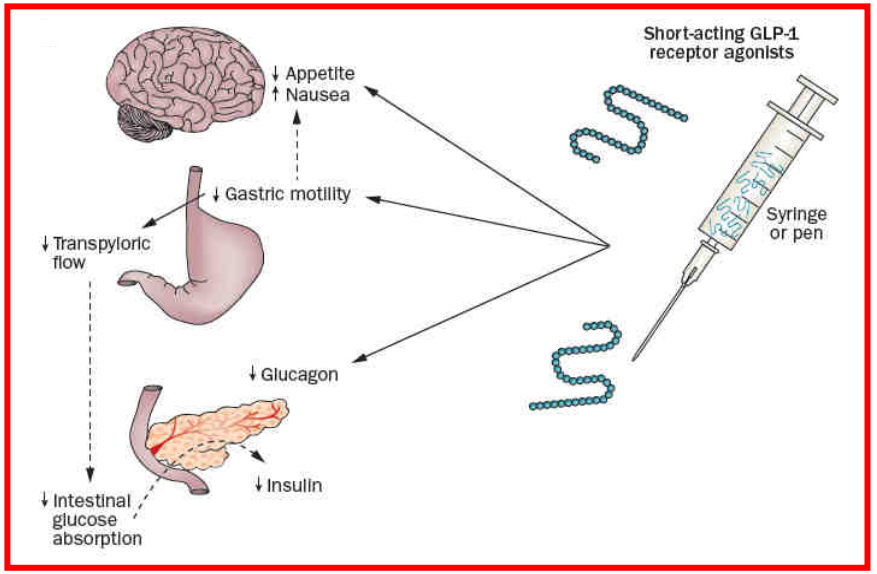
S. Madsbad et al. Diabetes, Obesity and Metabolism 13: 394–407, 2011.

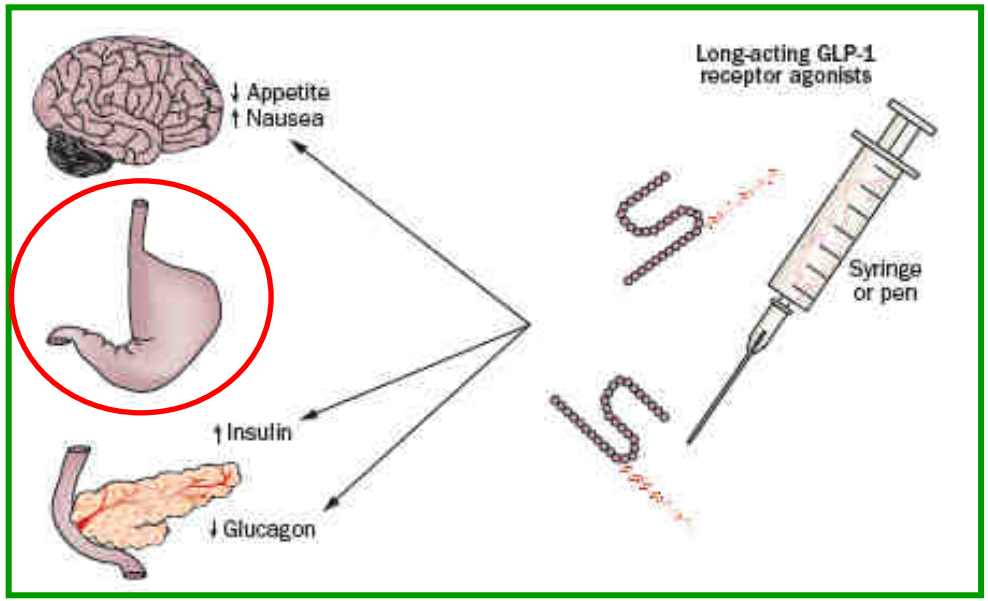


Meier, J. J. *Nat. Rev. Endocrinol. 8, 728–742 (2012)*

Physiological role of GLP-1 and proposed working models for the actions of long-acting GLP-1 receptor agonists in the postprandial state.



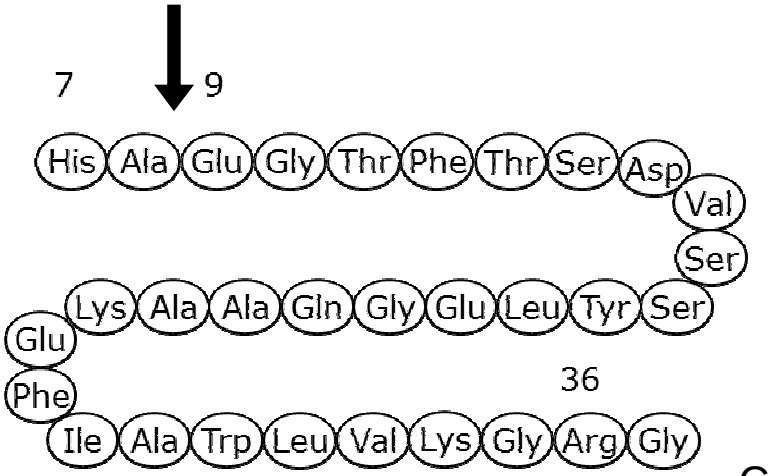




Liraglutide, analogo once-daily del GLP-1 umano

GLP-1 umano nativo

Sito di degradazione del DPP-4

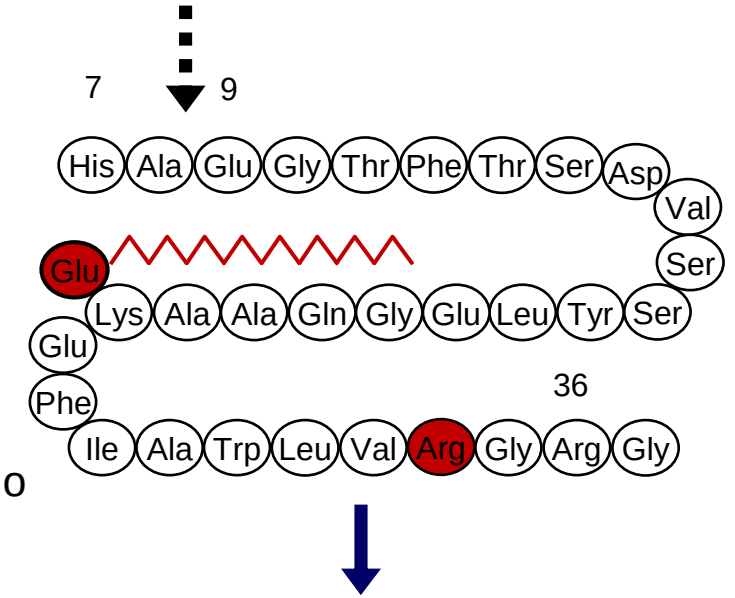


$T_{½}$=1.5–2.1 min

Catena di acido grasso C-16 (palmitico)

Liraglutide

Sito di degradazione del DPP-4

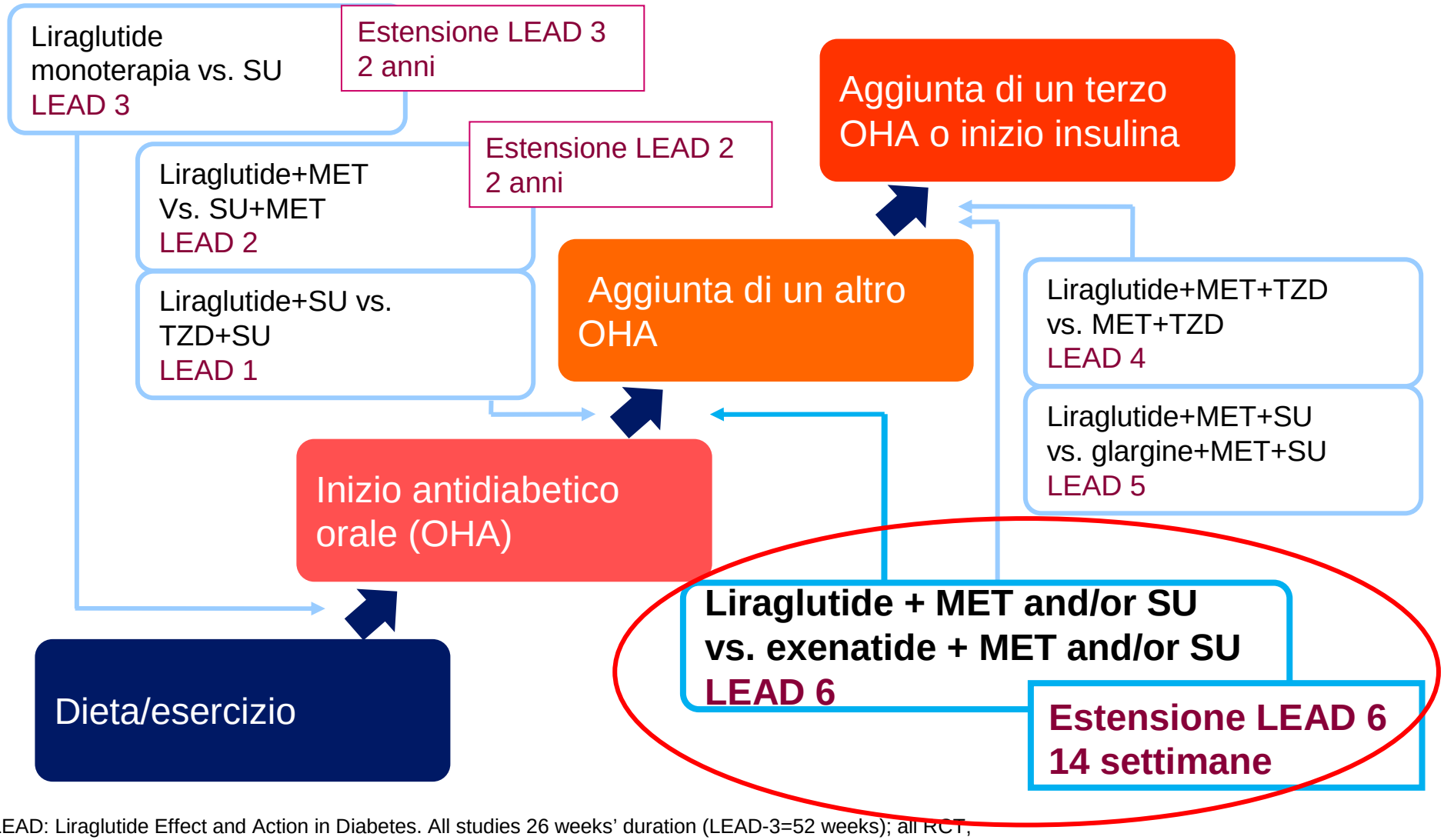


- 97% di omologia con il GLP-1 nativo
- legame all'albumina plasmatica
- lento assorbimento dal sottocute
- resistenza al DPP-IV
- lunga emivita plasmatica

$T_{½}$=13 ore

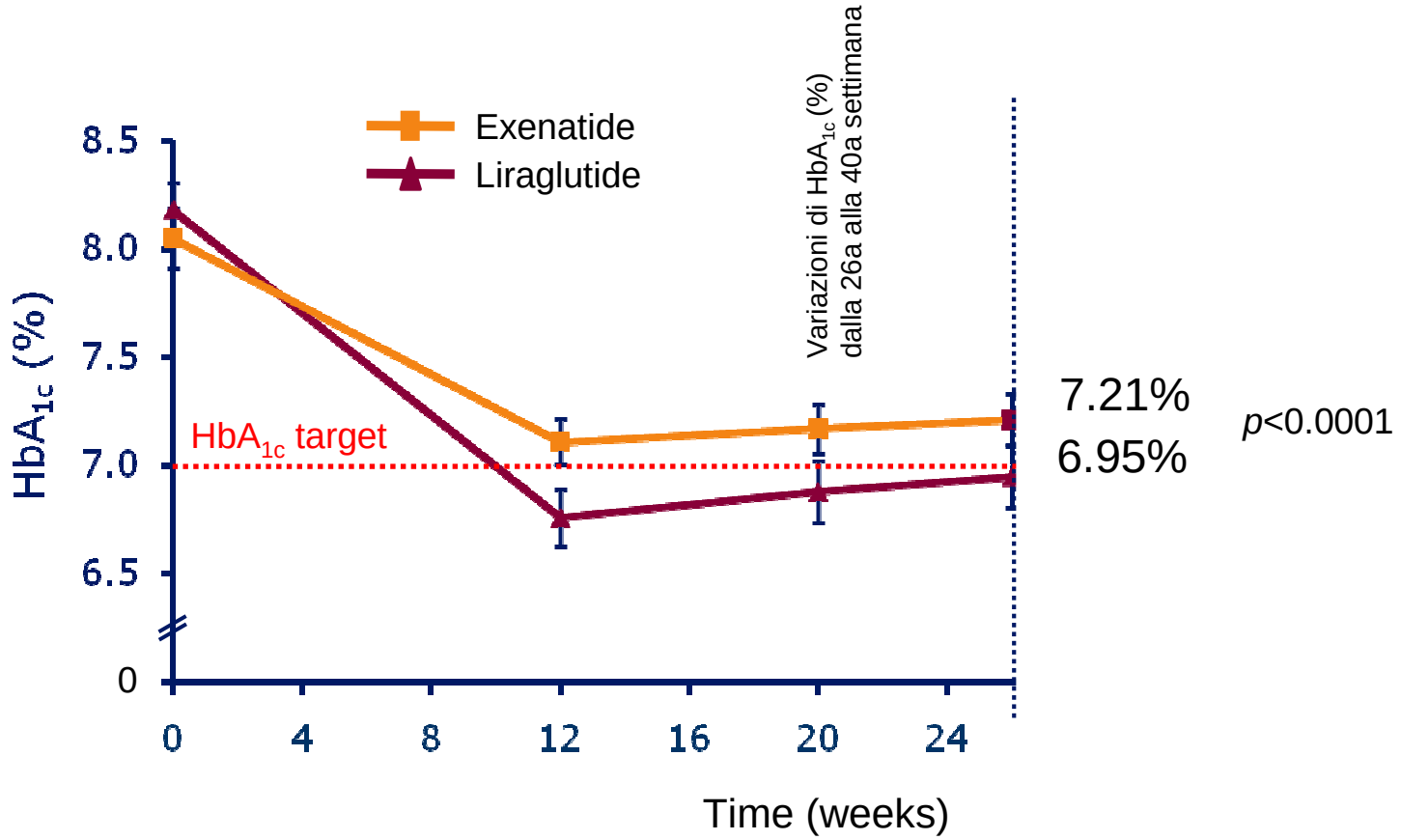
Agersø *et al. Diabetologia* 2002; 45:195–202
Knudsen *et al. J Med Chem* 2000; 43:1664–9
Degn *et al. Diabetes* 2004; 53:1187–94
Vilsbøll *et al. J Clin Endocrinol Metab* 2003;88(1):220–4

LEAD: “Liraglutide Effect and Action in Diabetes”



LEAD: Liraglutide Effect and Action in Diabetes. All studies 26 weeks’ duration (LEAD-3=52 weeks); all RCT; Marre et al. Diabetic Medicine 2009;26;268–78 (LEAD-1); Nauck et al. Diabetes Care 2009;32;84–90 (LEAD-2); Garber et al. Lancet 2009;373:473–81 (LEAD-3); Zinman et al. Diabetes Care 2009;32:1224–30 (LEAD-4); Russell-Jones et al. Diabetologia 2009;52:2046-2055 (LEAD-5); Buse et al. Lancet 2009;374 (9683):39–47 (LEAD-6)

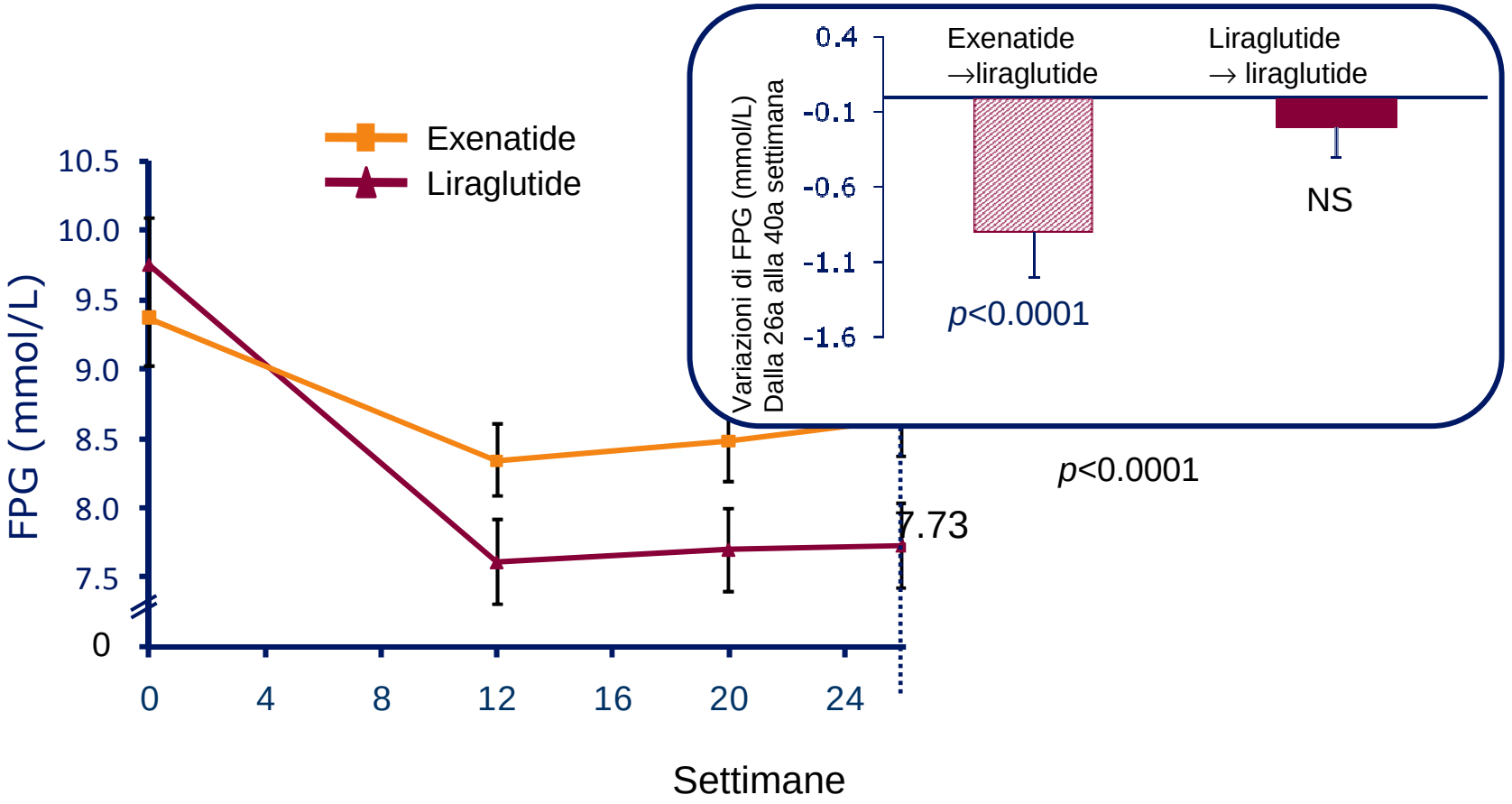
Liraglutide vs exenatide: efficacia su HbA1c



I dati per le settimane 0-26 sono solo per i soggetti che hanno partecipato alla fase di estensione dello studio

Buse *et al. Lancet* 2009;374(9683):39–47 (LEAD-6); Buse *et al. Diabetes* Care March 23, 2010, doi: 10.2337/dc09-2260 (LEAD-6 Ext)

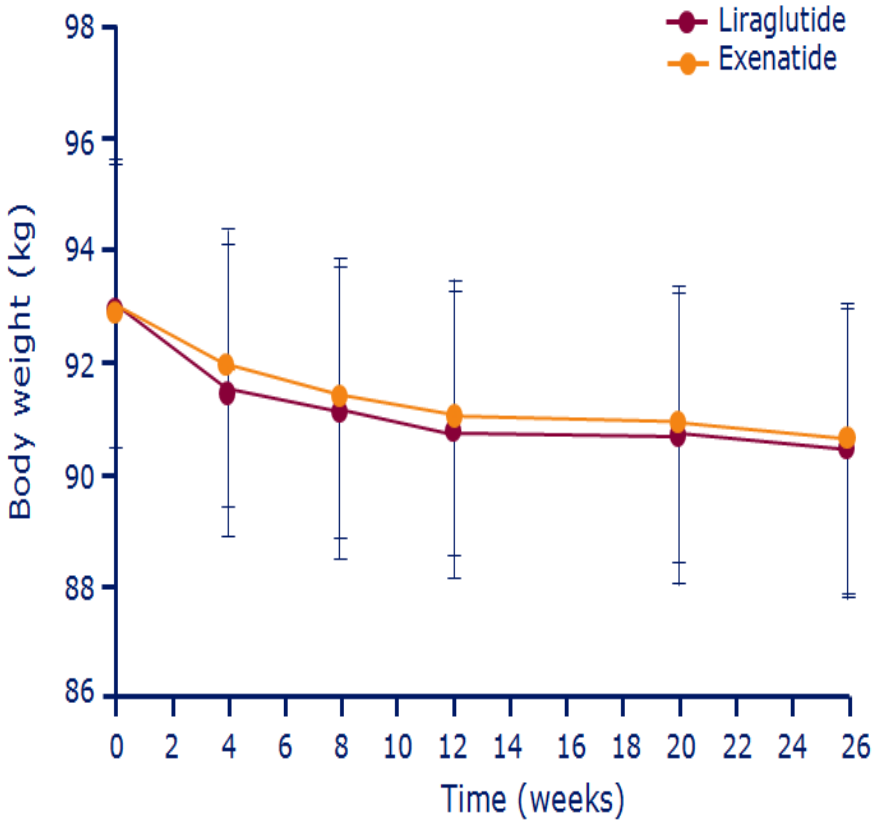
Liraglutide vs exenatide: efficacia su FPG

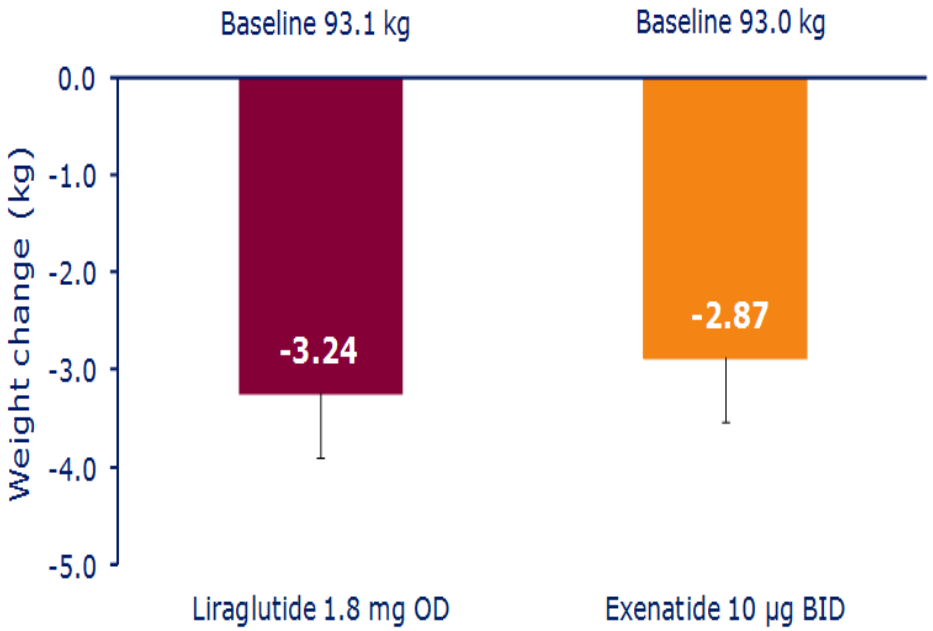


Media (2 SE)
I dati per le settimane 0-26 sono solo per i soggetti che hanno partecipato alla fase di estensione dello studio

Buse *et al. Lancet* 2009;374(9683):39–47 (LEAD-6); Buse *et al. Diabetes* Care March 23, 2010, doi: 10.2337/dc09-2260 (LEAD-6 Ext)

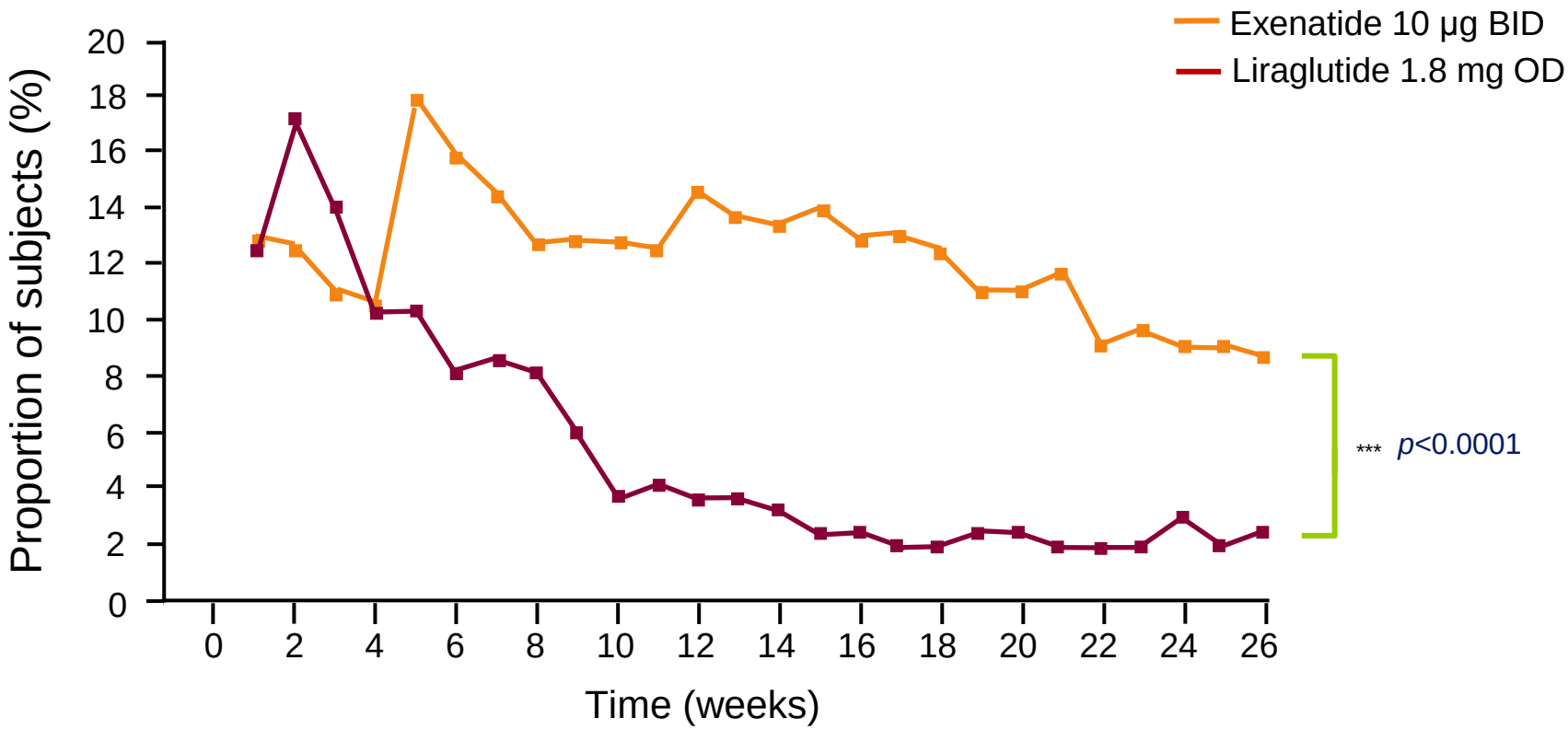
Direct comparison of liraglutide and exenatide: change in body weight





Buse *et al. Lancet* 2009;374:39–47 (LEAD-6)

Direct comparison of liraglutide and exenatide: reports of nausea by week



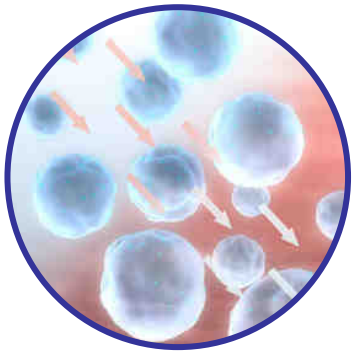
***$p<0.0001$ for treatment differences (estimated treatment rate ratio for liraglutide vs. exenatide, 0.448)

Data are number (%) of patients exposed to treatment (safety population)

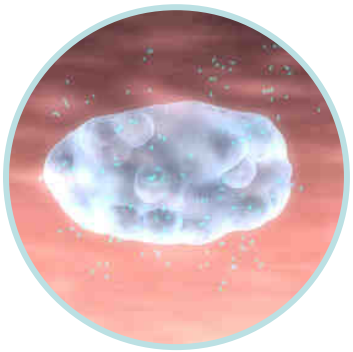
Buse *et al. Lancet* 2009;374:39–47 (LEAD-6)

Development of Exenatide once-weekly

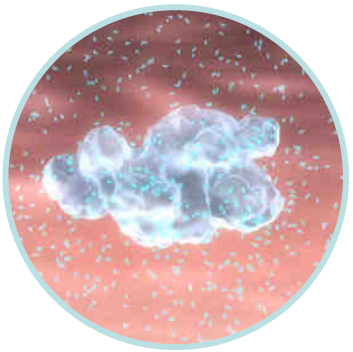
- Patented Medisorb® microspheres are a biodegradable polymer that dissipates into CO_2 and water[1]
- The microspheres deliver a constant presence of exenatide with a single weekly dose[1]
- It takes about 2 weeks to achieve concentrations in the therapeutic range[2]
- Steady-state exenatide concentration is reached at 6–7 weeks[2]



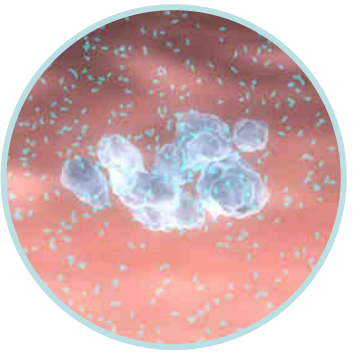
Subcutaneous injection of microsphere suspension of exenatide[1]



Individual microspheres aggregate and initial release of exenatide[1]



Microsphere degradation and continued release of exenatide[1]



Further degradation and metabolism of microsphere polymer provide a sustained level of exenatide[1]

1. DeYoung MB, et al. *Diabetes Technol Ther*. 2011;13:1145-1154; 2. Kim D, et al. *Diabetes Care*. 2007;30:1487-1493.

Development of Exenatide once-weekly

EQW was developed using microsphere drug delivery technology to improve:

- Fasting 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)

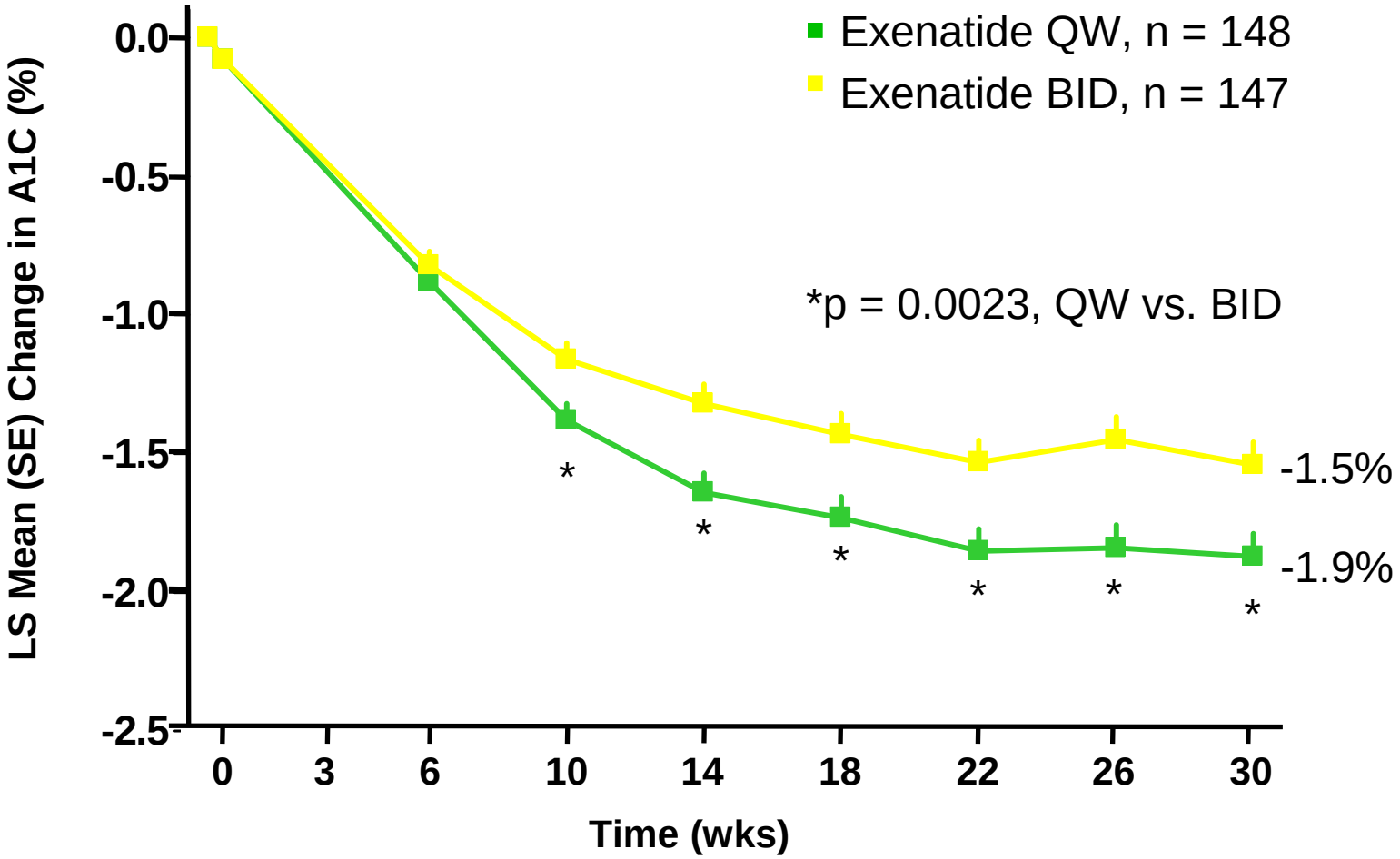
1. **Malone J, et al. *Expert Opin Investig Drugs*. 2009;18:359-367.**
2. **Tracy MA, et al. *Biomaterials.* 1999;20:1057-1062.**

exenatide QW clinical trials

Trial	Comparator	Background	Subjects	Publication
DURATION-1	Exenatide BID Open-label	Drug-naïve, mono and combo failures	295	Drucker, et al. *Lancet.* 2008
DURATION-2	Sitagliptin (100 mg QD) or pioglitazone (45 mg QD) Double-blind	Metformin	491	Bergenstal, et al. *Lancet*. 2010
DURATION-3	Insulin glargine Open-label	Metformin +/- sulphonylurea	456	Diamant, et al. *Lancet*. 2010
DURATION-5	Exenatide BID Open-label	Drug-naïve, mono and combo failures	252	Blevins, et al. *J Clin Endocrin Metab*. 2011
DURATION-6	Liraglutide 1.8 mg Open-label	Mono and combo failures	911	Buse, et al. *Lancet*. 2012

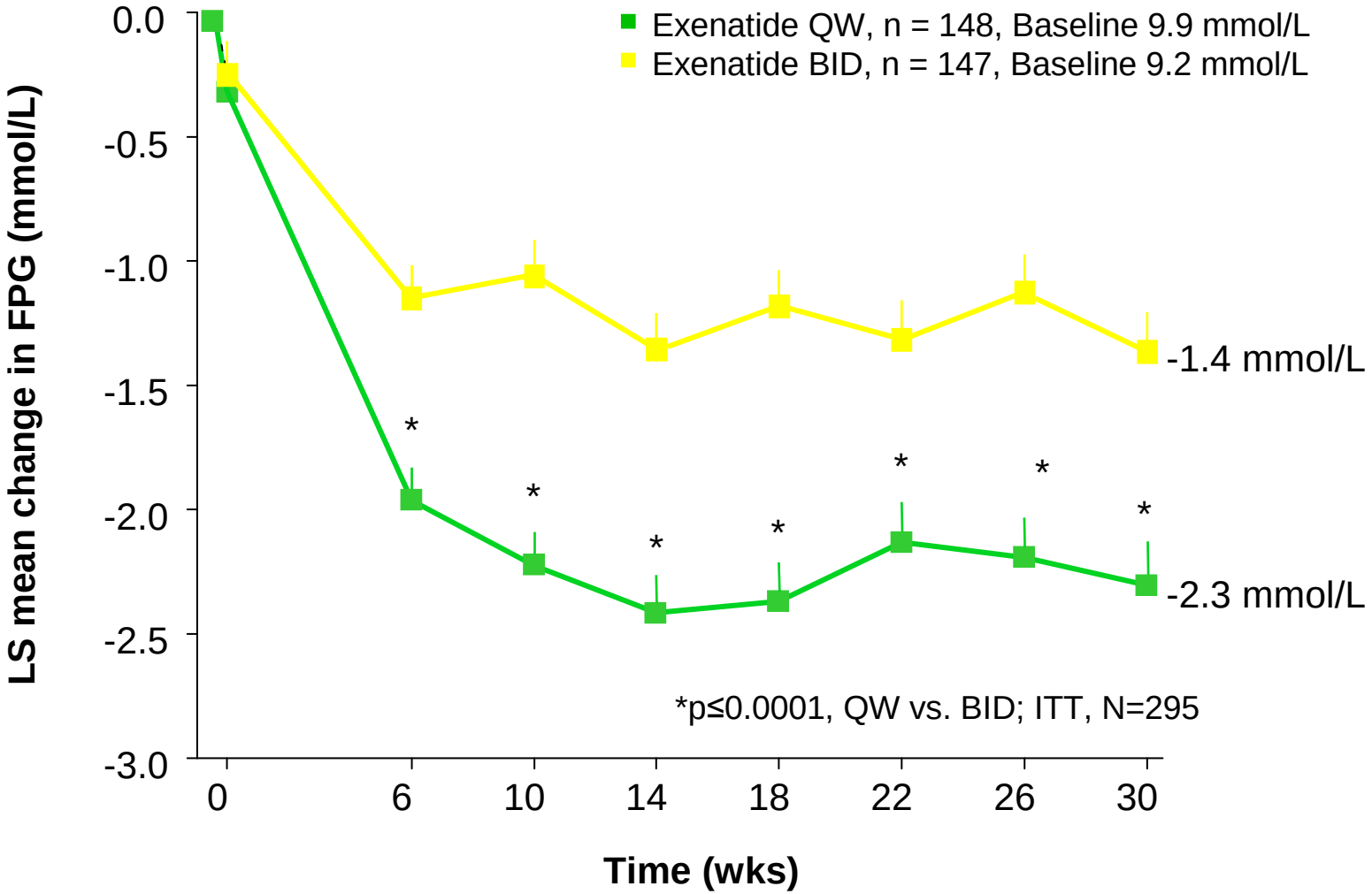
The DURATION-4 clinical trial of exenatide QW monotherapy vs metformin, sitagliptin, or pioglitazone monotherapy was conducted in adult patients uncontrolled on diet and exercise alone. exenatide QW is not indicated as first-line monotherapy in patients uncontrolled on diet and exercise alone.

Efficacy of Exenatide QW versus Exenatide BID: Change in A_{1C} from Baseline Over 30 Weeks



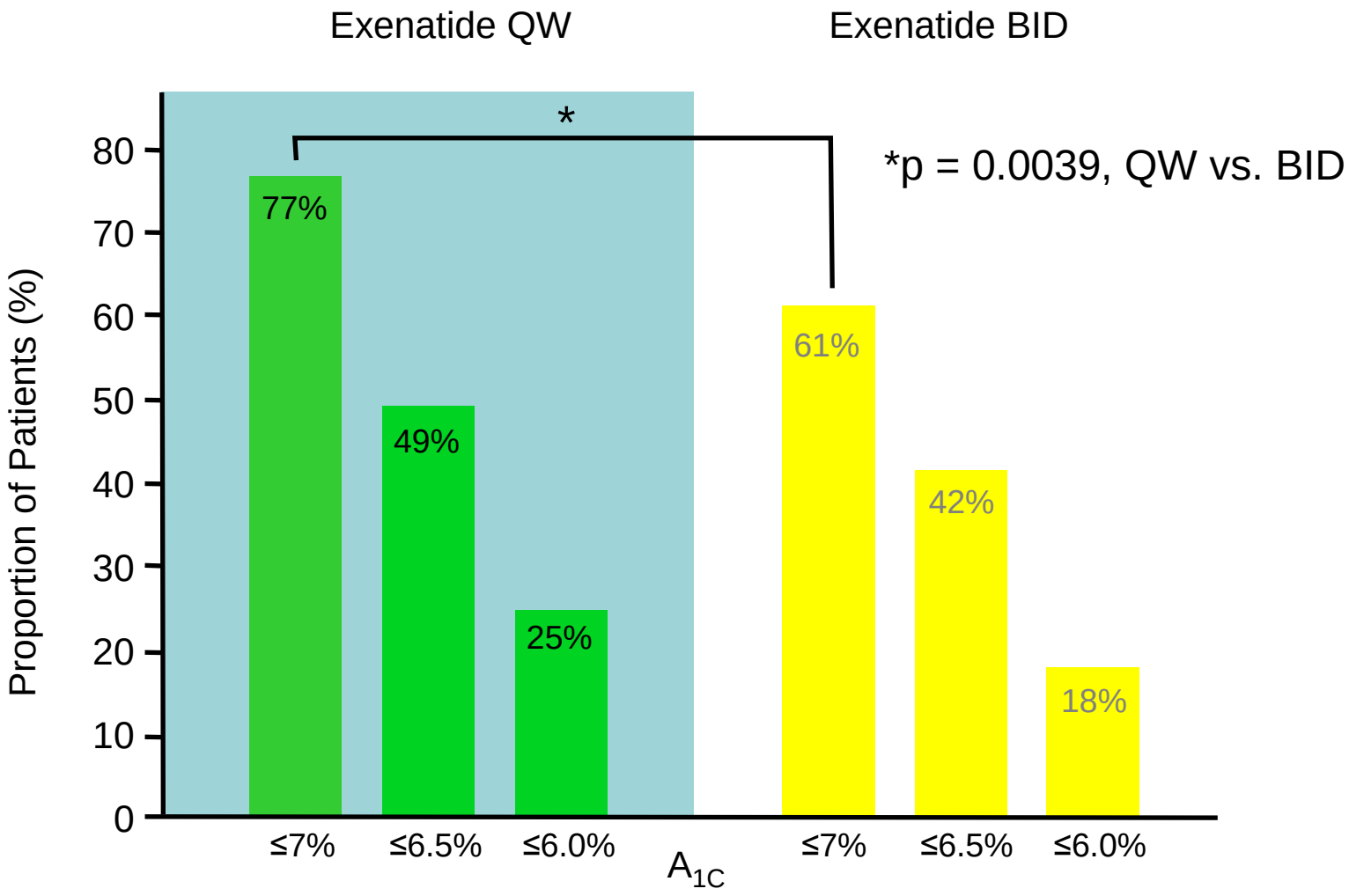
Drucker DJ, et al. *The Lancet*. 2008; 372:1240-1250

Change in Fasting Plasma Glucose From Baseline Over 30 Weeks



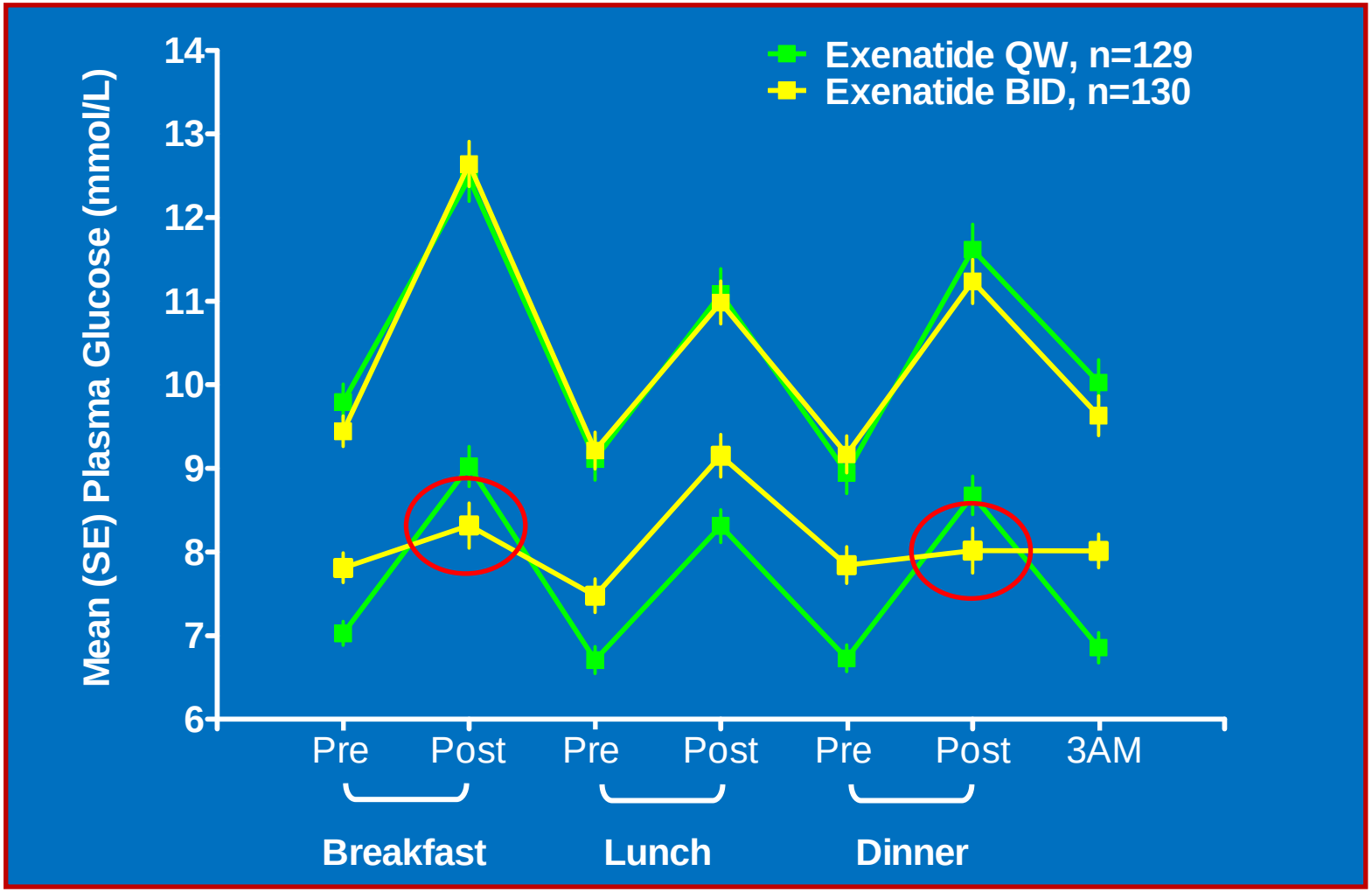
Drucker DJ, et al. *The Lancet*. 2008; 372:1240-1250

Percentage of Evaluable Patients (N = 259) Achieving HbA_{1c} ≤7, ≤6.5, ≤6.0 at Week 30



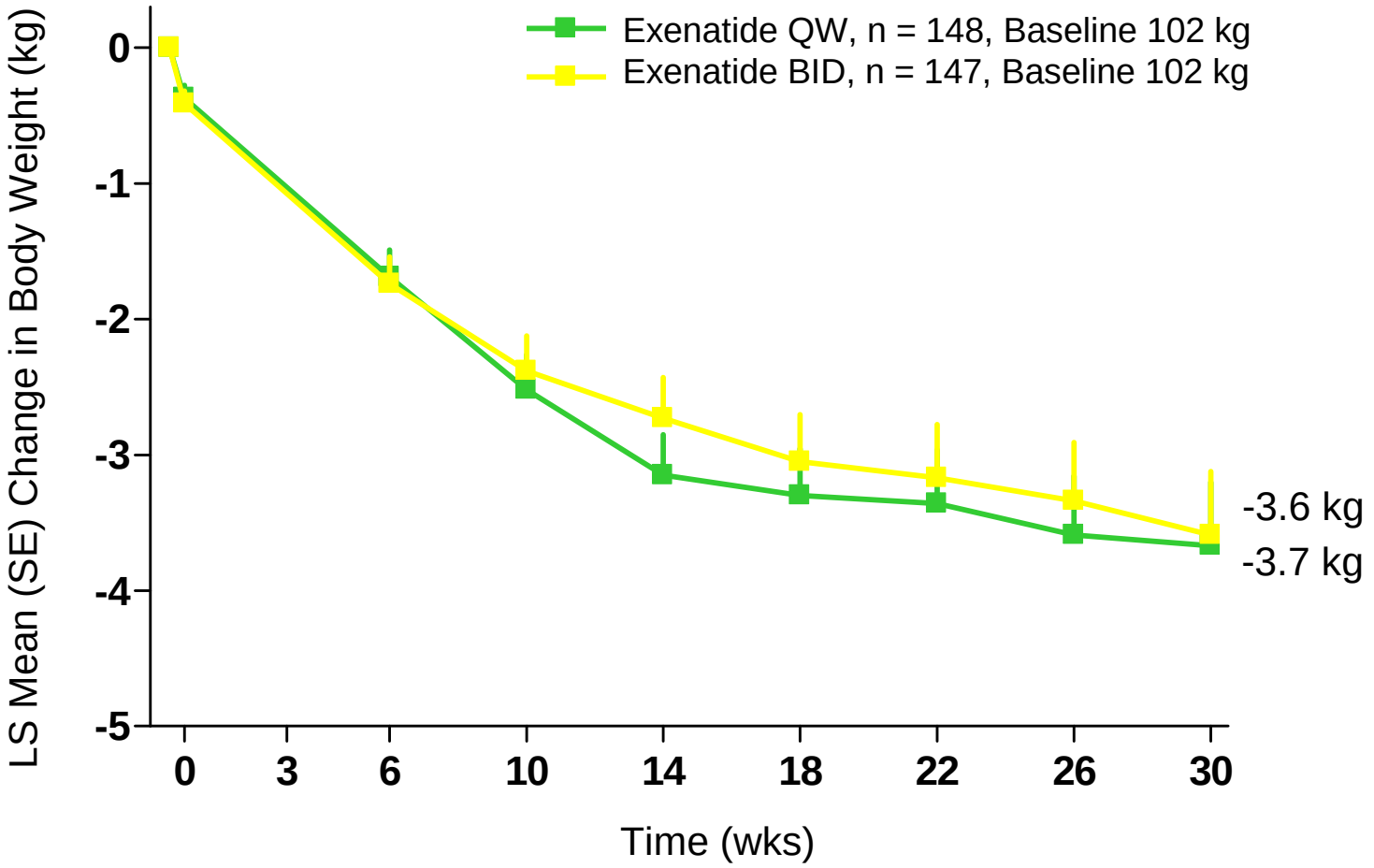
Drucker DJ, et al. *The Lancet*. 2008; 372:1240-1250

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

Change in Body Weight From Baseline Over 30 Weeks



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

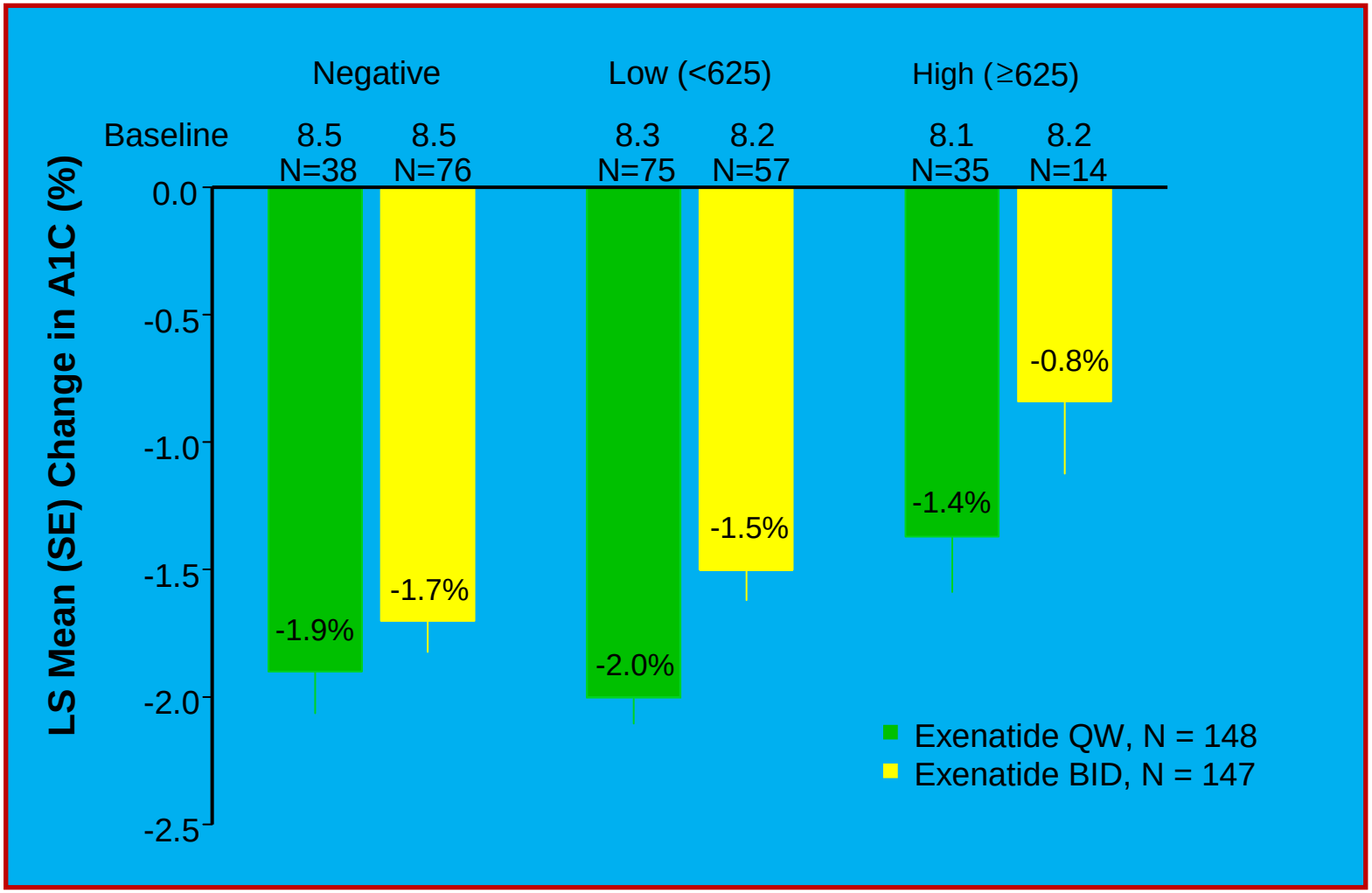
Overall Incidence of Treatment-emergent Adverse Events Occurring in 10% or More of Patients*

	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

Change in A_{1C} by Antibody Status Over 30 Weeks



Low titre ≤1/625 at any point during the 30 weeks; high titre ≥1/625 at any point during the 30 weeks

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

Weight-Related Quality of Life, Health Utility, Psychological Well-Being, and Satisfaction With Exenatide Once Weekly Compared With Sitagliptin or Pioglitazone After 26 Weeks of Treatment

Best JH et al. Diabetes Care 2011, 34:314–319

Table 2—*Baseline and change from baseline to week 26 in IWQOL-Lite, PGWB, DTSQ-s, and EQ-5D among subjects with type 2 diabetes participating in a randomized, multicenter, double-dummy study of treatment with exenatide QW, sitagliptin, or pioglitazone (intent-to-treat population)*

	Exenatide QW				Sitagliptin				Pioglitazone			
	n†	Baseline	Change‡	95% CI	*n*†	Baseline	Change‡	95% CI	*n*†	Baseline	Change‡	95% CI
IWQOL-Lite												
Total score	132	80.67	5.15* (1.04)	3.11–7.19	139	80.74	4.56* (1.02)	2.56–6.57	130	79.32	1.20§ (1.06)	−0.87–3.28
Physical function	133	73.37	6.78* (1.35)	4.11–9.44	141	73.75	5.81* (1.33)	3.20–8.42	131	73.00	2.00§ (1.38)	−0.71–4.71
												4–5.89
												9–5.60
												6–1.70
												2–1.26
												1–0.06
												6–5.24
												7–6.79
												8–7.73
												6–6.40
												7–7.88
Self control	133	75.11	5.53* (1.37)	2.83–8.22	141	78.71	4.30* (1.34)	1.67–6.94	130	83.33	3.68* (1.40)	0.93–6.43
General health	133	65.39	9.46* (1.40)	6.72–12.21	141	67.84	6.95* (1.37)	4.26–9.65	130	67.56	6.37* (1.43)	3.56–9.17
Vitality	133	61.20	7.46* (1.37)	4.76–10.16	141	63.51	8.98* (1.35)	6.33–11.63	130	65.00	6.23* (1.41)	3.46–9.00
DTSQ												
Total score	121	27.99	3.96* (0.60)	2.78–5.15	127	28.13	2.35* (0.59)	1.19–3.51	123	26.78	2.50* (0.61)	1.31–3.69
Perceived frequency high blood glucose	121	3.84	−1.63* (0.17)	−1.96 to −1.30	127	3.94	−1.30* (0.17)	−1.63 to −0.97	123	3.56	−1.28* (0.17)	−1.62 to −0.94
Perceived frequency low blood glucose	120	0.94	0.22 (0.15)	−0.07 to 0.51	126	1.12	−0.05 (0.15)	−0.33 to 0.24	122	0.91	−0.12 (0.15)	−0.42 to 0.17

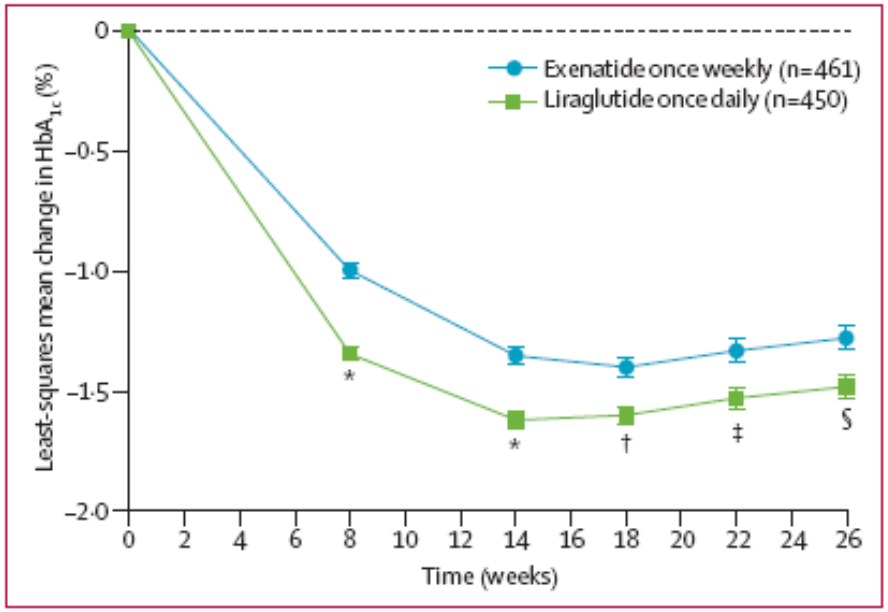
†Number of subjects with a baseline and postrandomization score. ‡Data are least squares mean changes (and SE). *$P \leq 0.05$ (change from baseline within treatment group). §$P \leq 0.05$ (difference compared with exenatide group at week 26).

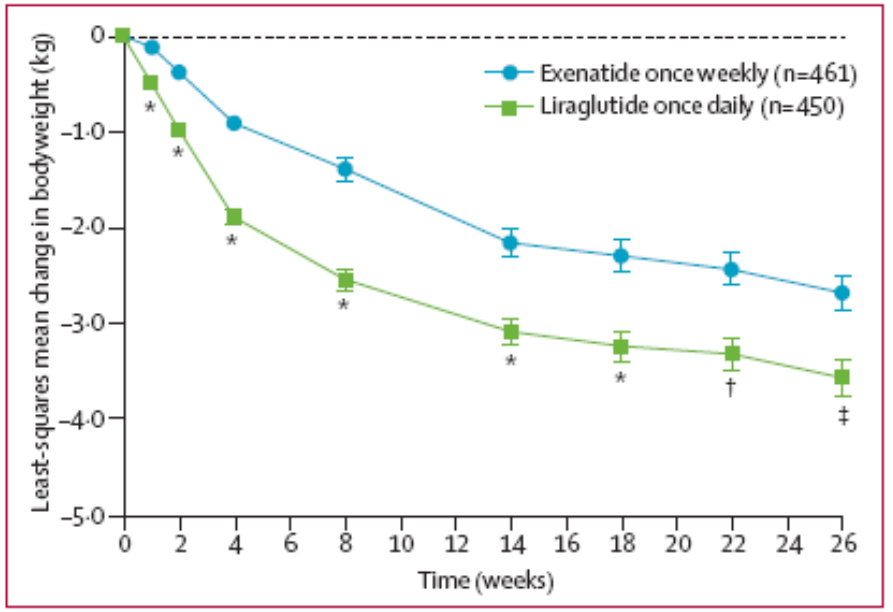
Conclusions: In this study exenatide QW treatment was associated with important clinical benefits, QOL and treatment satisfaction

Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study

John B Buse, Michael Nauck, Thomas Forst, Wayne H-H Sheu, Sylvia K Shenouda, Cory R Heilmann, Byron J Hoogwerf, Aijun Gao, Marilyn K Boardman, Mark Fineman, Lisa Porter, Guntram Schernthaner

Lancet 2013; 381: 117–24





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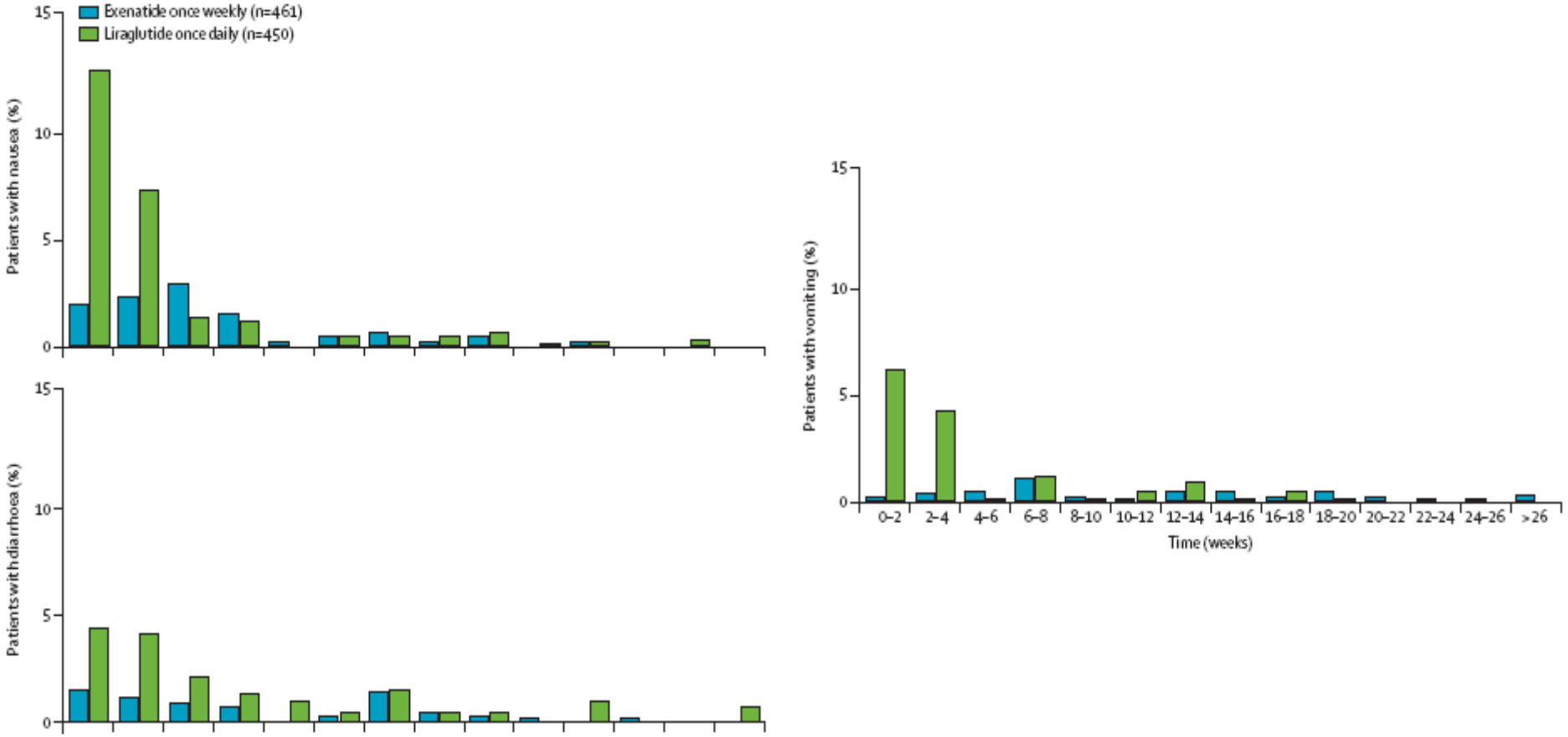


Diabetes Obes Metab. 2013 Mar;15(3):213-23.

A network meta-analysis to compare glycaemic control in patients with type 2 diabetes treated with exenatide once weekly or liraglutide once daily in comparison with insulin glargine, exenatide twice daily or placebo.

Scott DA, Boye KS, Timlin L, Clark JF, Best JH.

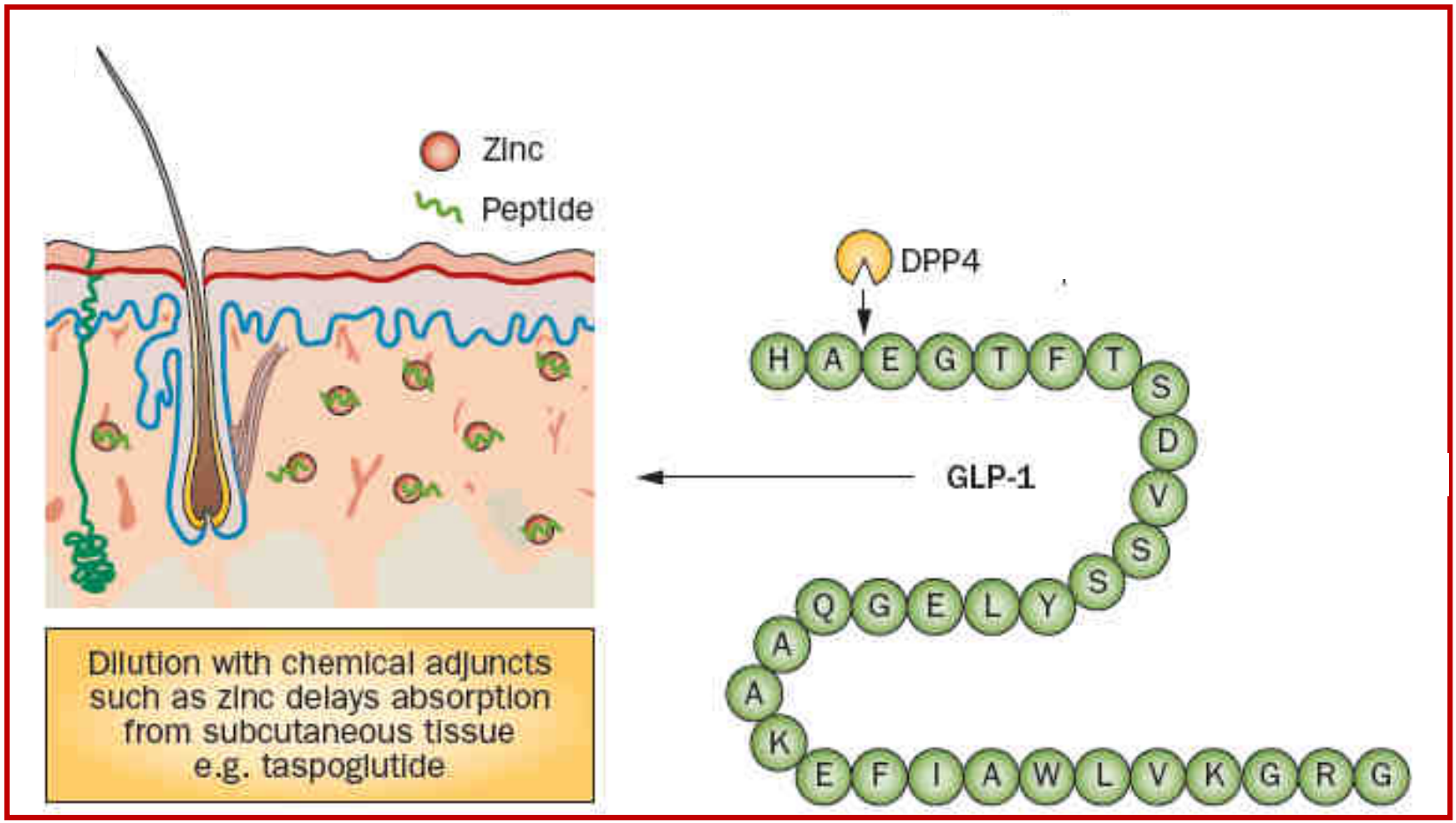
AIMS: The glucagon-like peptide-1 receptor agonists (GLP-1 RAs) exenatide once weekly (ExQW) and liraglutide once daily (QD) are indicated to improve glycaemic control in patients with type 2 diabetes. Although glycaemic control with ExQW versus liraglutide QD 1.8 mg has been directly compared, no studies have compared ExQW with liraglutide QD 1.2 mg or determined the probable relative efficacies of various injectable therapies for glycaemic control; therefore, a network meta-analysis was performed to address these questions.

METHODS: A systematic review identified randomized controlled trials of ≥24 weeks that compared ExQW, liraglutide QD (1.2 mg, 1.8 mg), insulin glargine, exenatide twice daily (ExBID), or placebo. Twenty-two studies evaluating 11 049 patients were included in the network meta-analysis. Mean differences in HbA1c relative to placebo or each other and probability rankings were estimated.

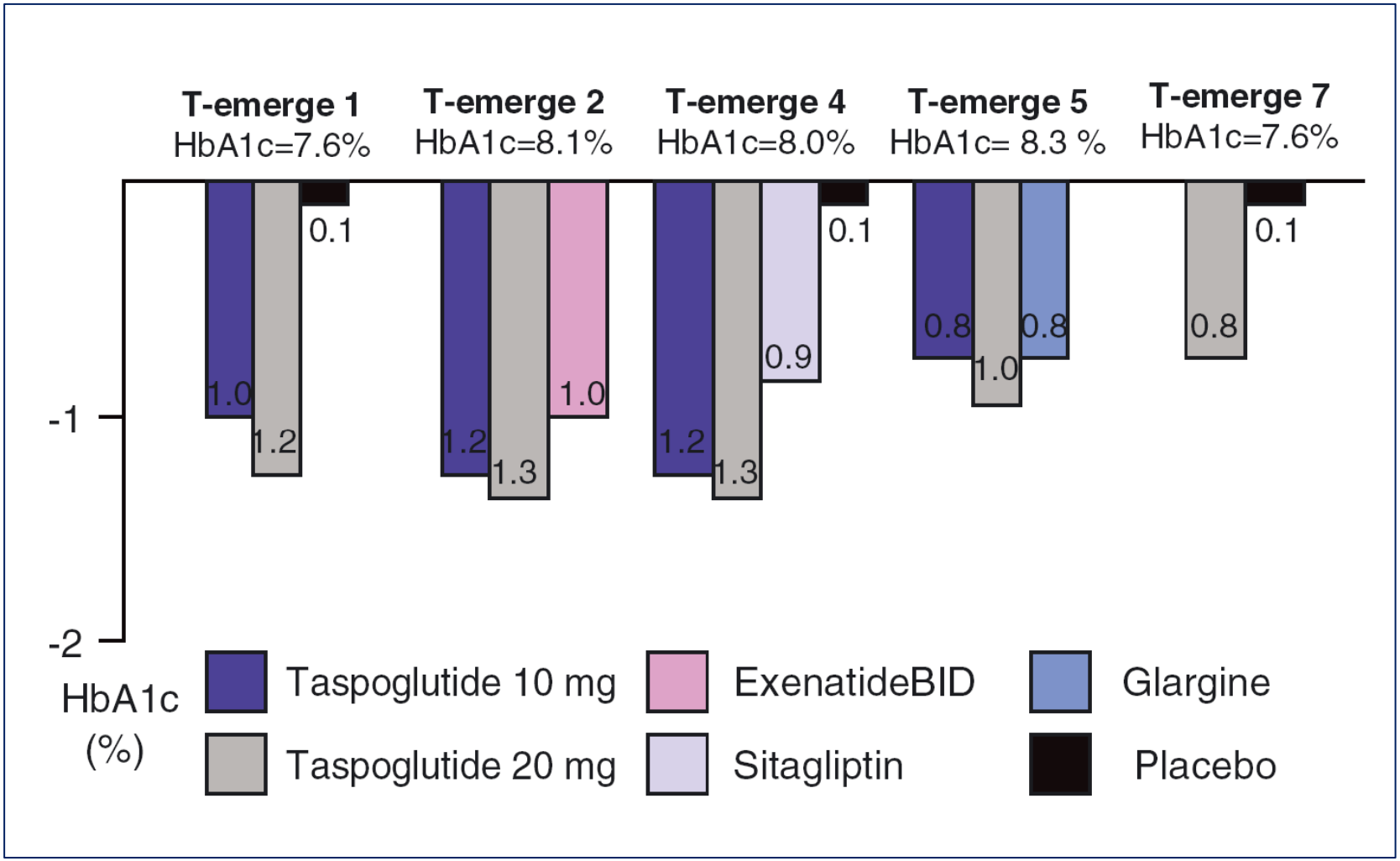
RESULTS: Estimated mean differences in HbA1c versus placebo were -1.15% (95% CrI: -1.31 to -1.00) for ExQW, -1.01% (95% CrI: -1.18 to -0.85) for liraglutide 1.2 mg, and -1.18% (95% CrI: -1.32 to -1.04) for liraglutide 1.8 mg. HbA1c differences for ExQW versus liraglutide 1.2 mg and 1.8 mg were -0.14% (95% CrI: -0.34 to 0.06) and 0.03% (95% CrI: -0.14 to 0.18), respectively. The estimated mean difference in HbA1c between liraglutide 1.2 mg and 1.8 mg was 0.17% (95% CrI: 0.02-0.30). Results were consistent when adjusted for background antihyperglycaemic medications and diabetes duration.

CONCLUSIONS: This network meta-analysis **did not identify meaningful differences in HbA1c lowering between ExQW and both liraglutide doses, suggesting that these GLP-1 RAs have similar glycaemic effects.**

TASPOGLUTIDE

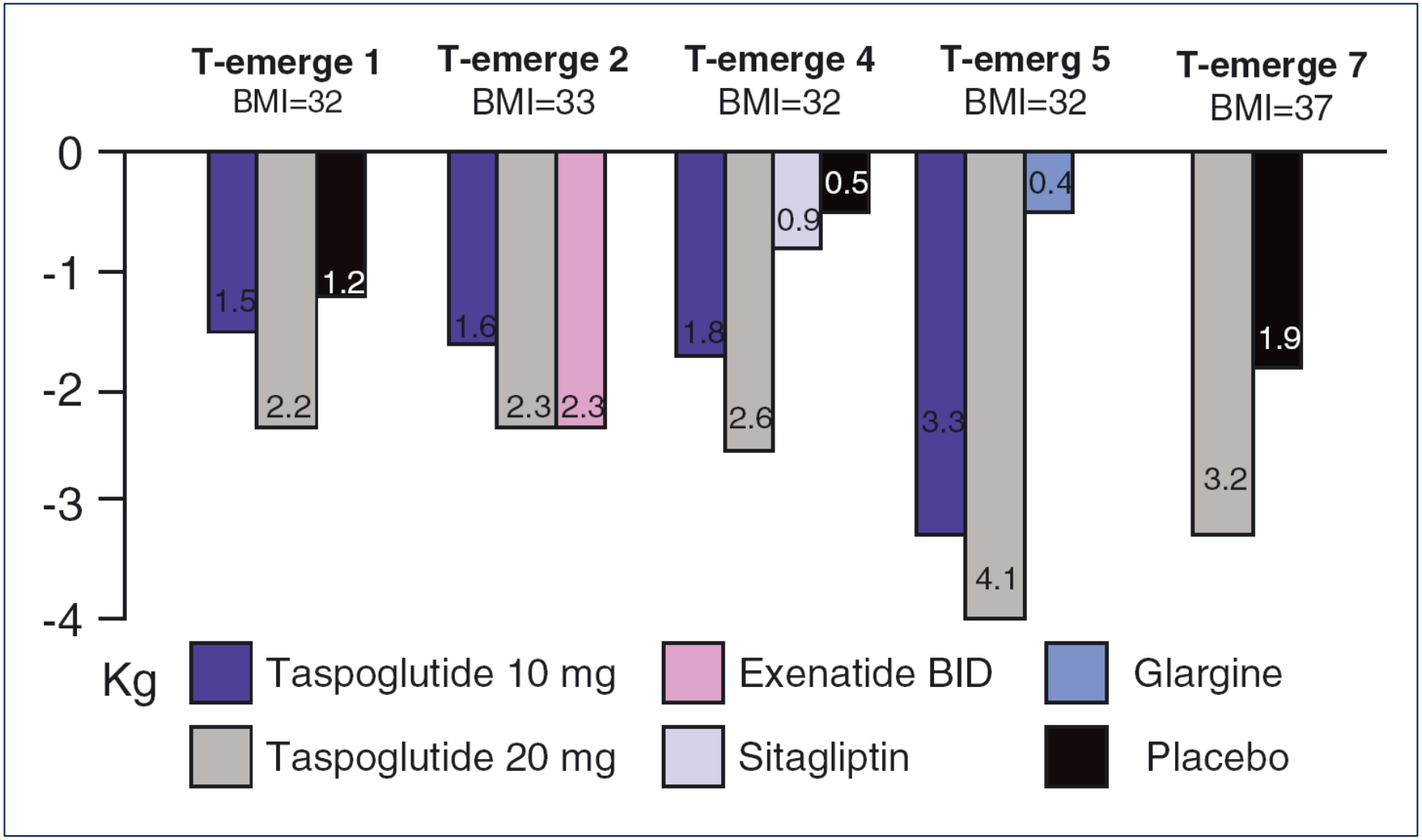


The effect on HbA1c of taspoglutide once weekly compared with placebo, oral antidiabetic agents and insulin glargine



S. Madsbad et al. Diabetes, Obesity and Metabolism 13: 394–407, 2011.

The effect on BW of taspoglutide once weekly compared with placebo, oral antidiabetic agents and insulin glargine



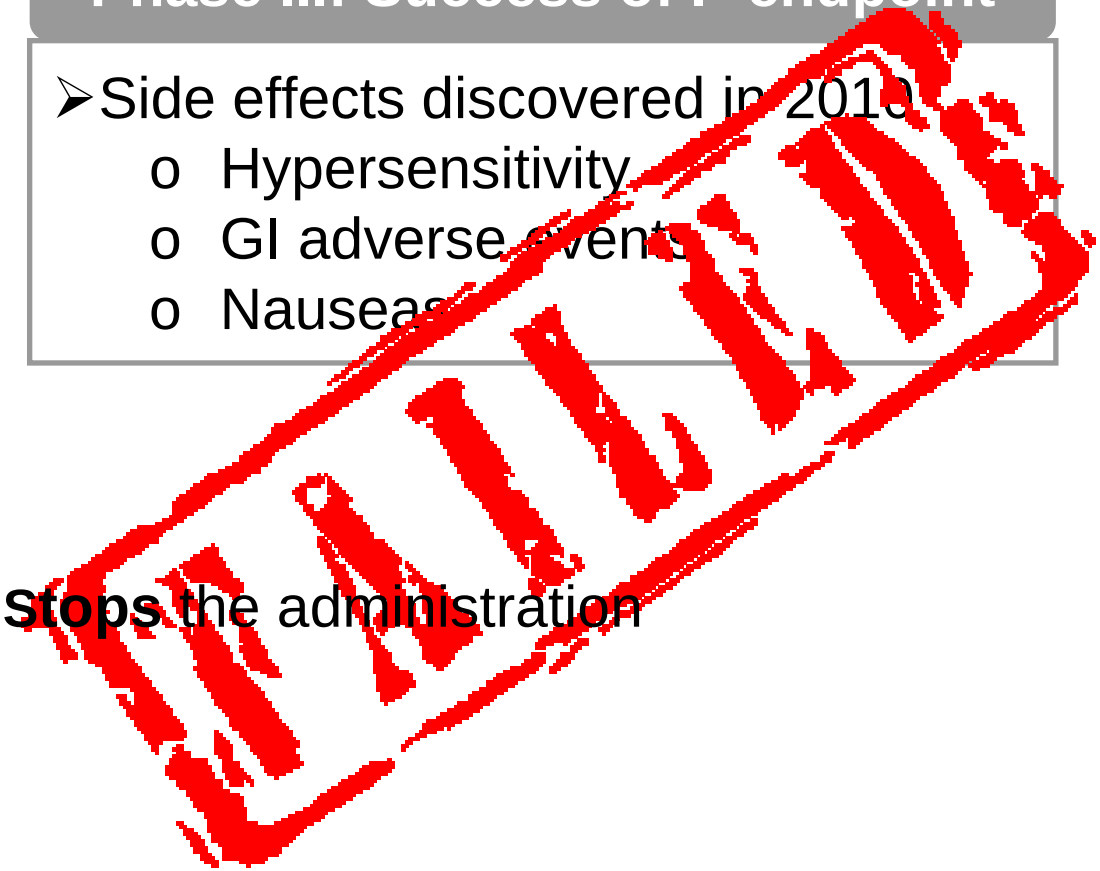
S. Madsbad et al. Diabetes, Obesity and Metabolism 13: 394–407, 2011.

TASPOGLUTIDE

2008

Phase III: Success of I° endpoint

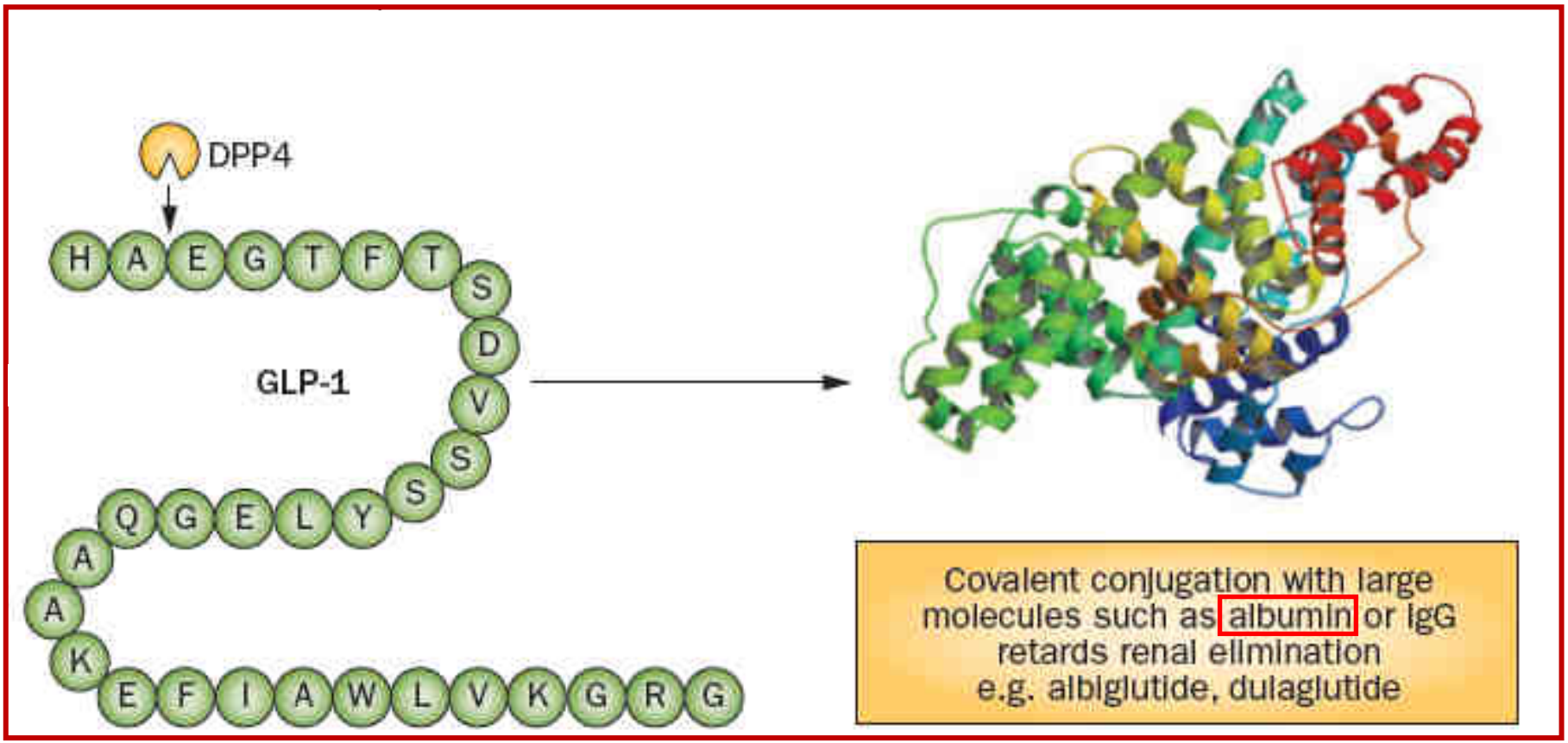
- Side effects discovered in 2010
  - Hypersensitivity
  - GI adverse events
  - Nauseas



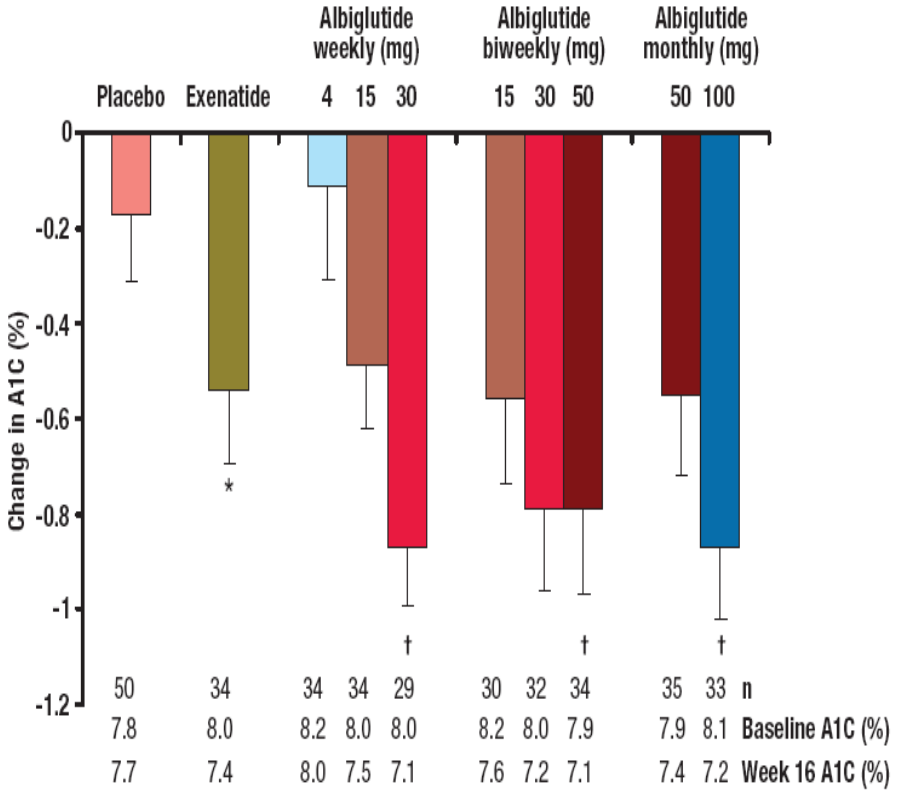
2011

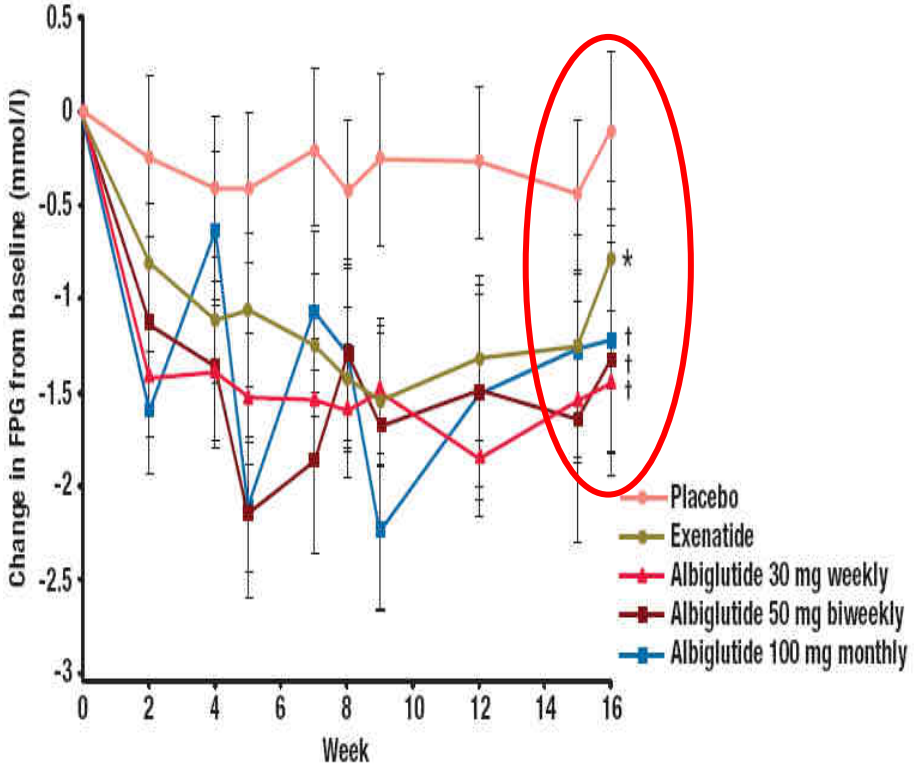
- **Stops** the administration

ALBIGLUTIDE



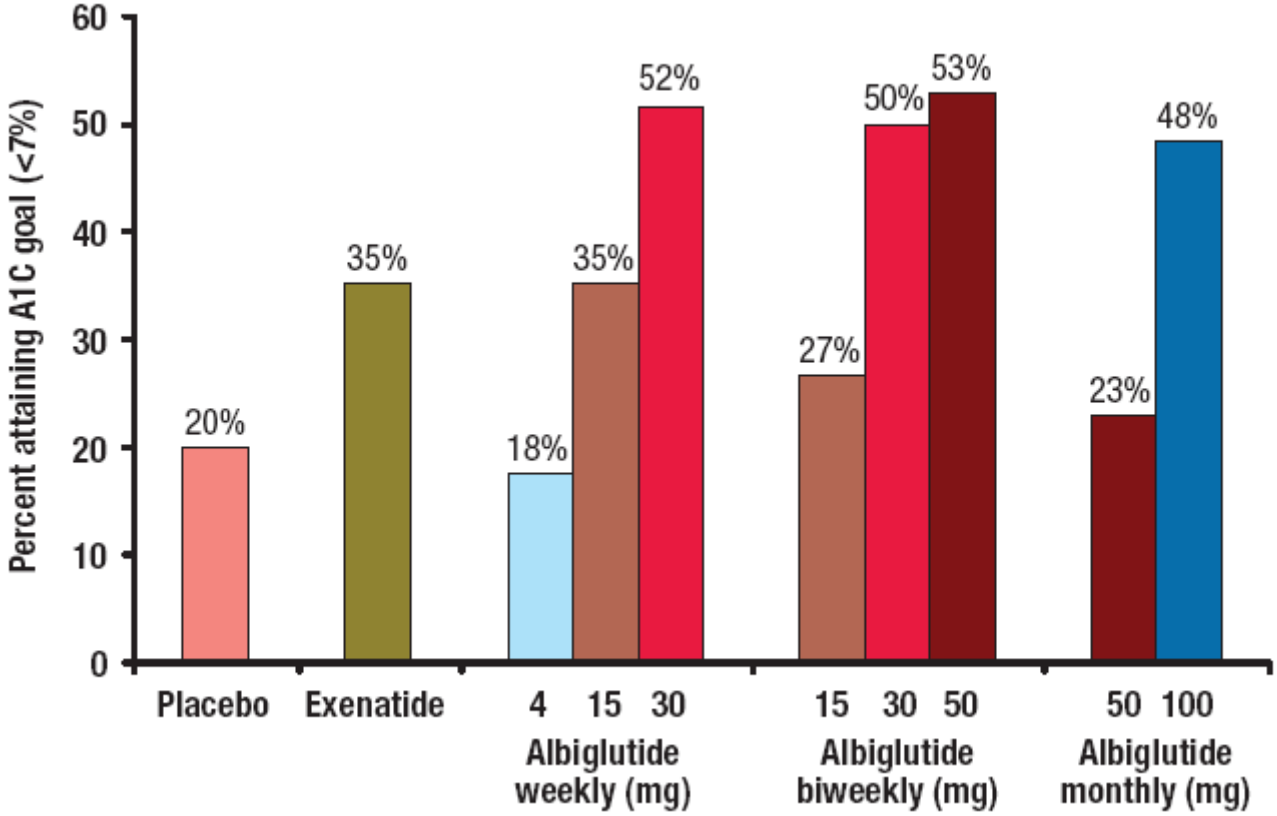
Potential of Albiglutide, a Long-Acting GLP-1 Receptor Agonist, in Type 2 Diabetes





Rosenstock J et al, *Diabetes Care 2009; 32:1880–1886*

Potential of Albiglutide, a Long-Acting GLP-1 Receptor Agonist, in Type 2 Diabetes



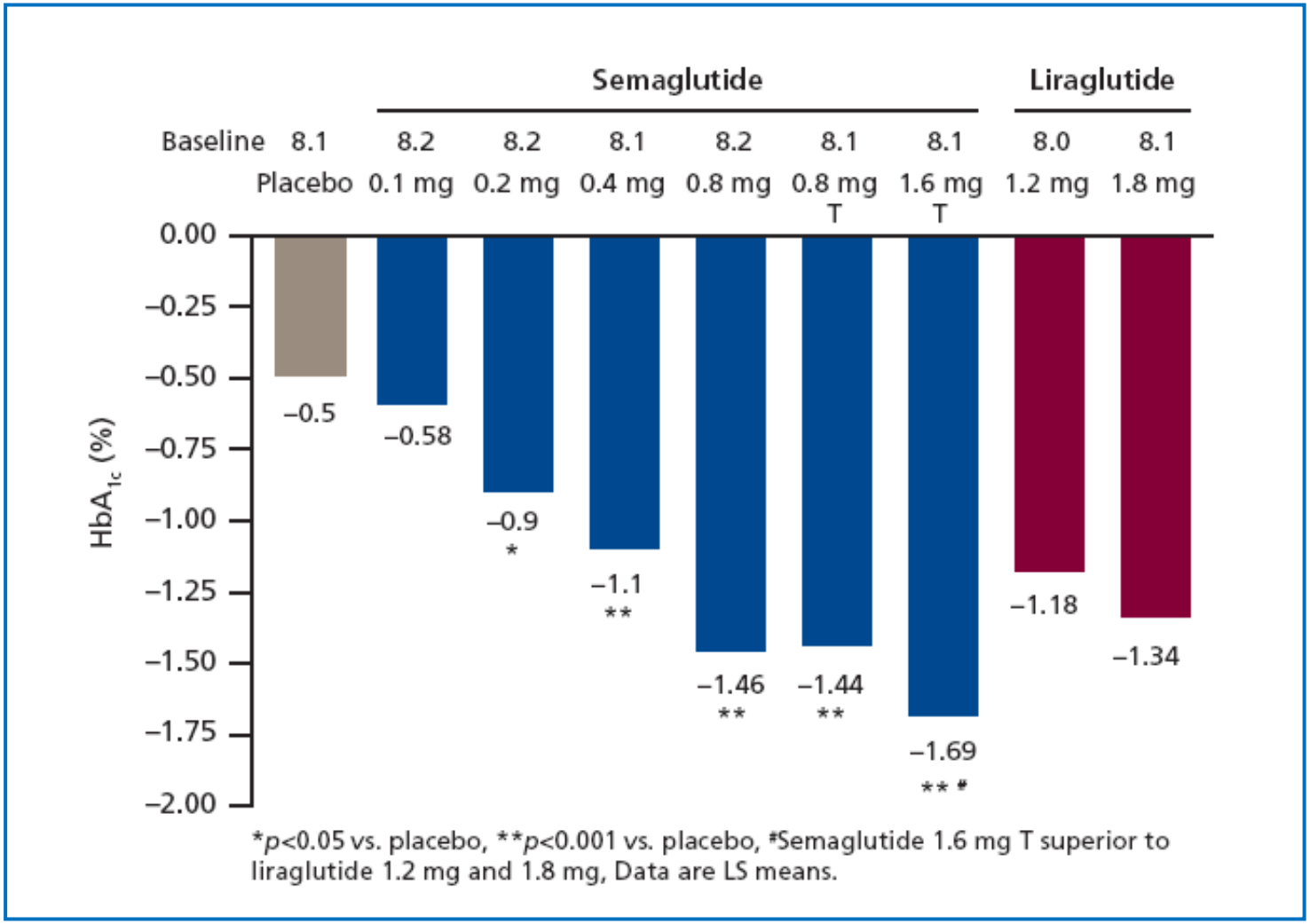
Rosenstock J et al, *Diabetes Care 2009; 32:1880–1886*

The once-weekly human GLP-1 analogues semaglutide provides significant reductions in HbA1c

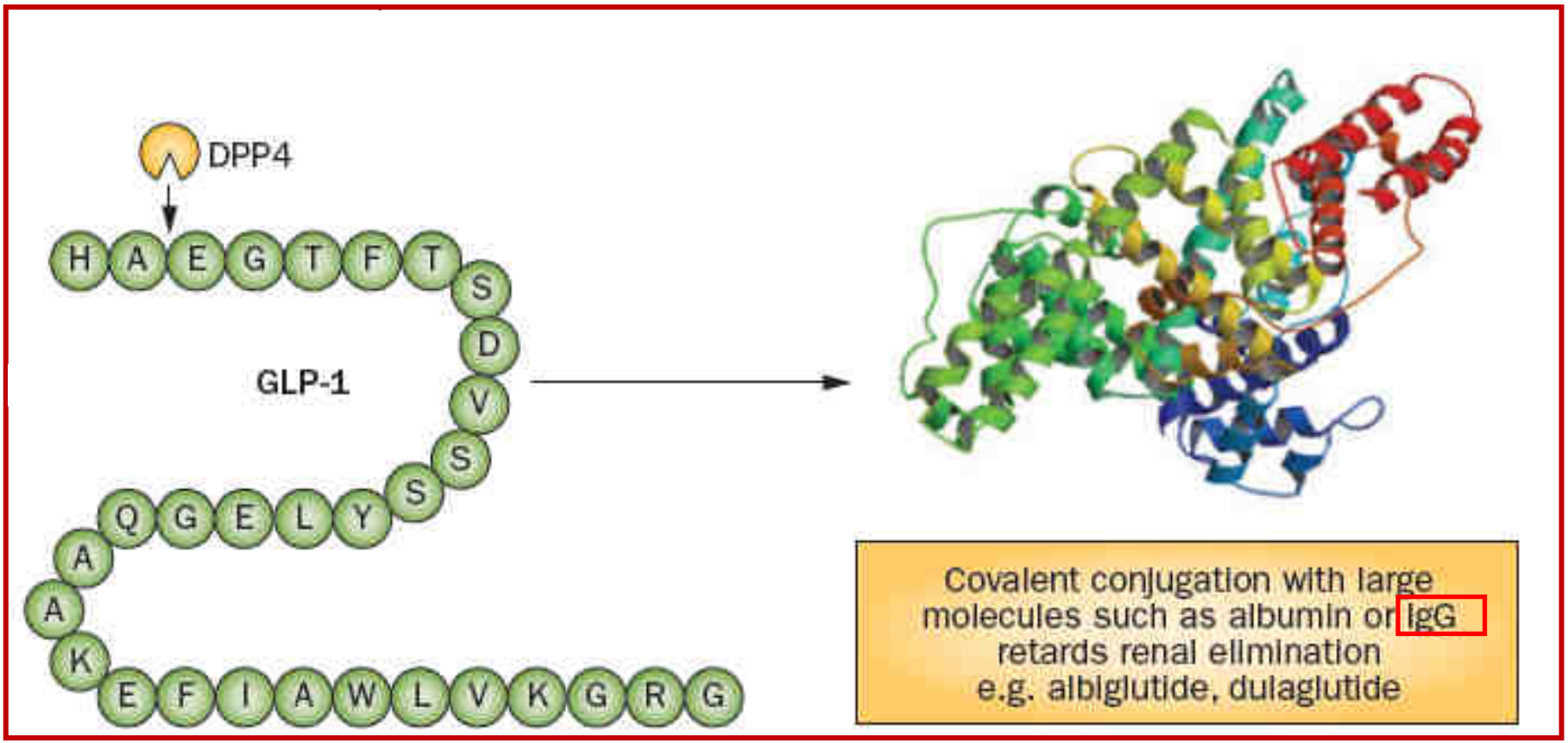
- **Semaglutide is a long-acting acylated human GLP-1 analogue under development, with pharmacokinetic (PK) properties suitable for once-weekly dosing (half life of 160 h).**

- **Medications administered once-weekly may have the potential to improve patient compliance and thereby treatment outcomes.**

The once-weekly human GLP-1 analogues semaglutide provides significant reductions in HbA1c



DULAGLUTIDE



Curr Opin Mol Ther. 2010 Dec;12(6):790-7.

Dulaglutide, a long-acting GLP-1 analog fused with an Fc antibody fragment for the potential treatment of type 2 diabetes.

Jimenez-Solem E, Rasmussen MH, Christensen M, Knop FK.

Abstract

Dulaglutide (LY-2189265) is a novel, long-acting glucagon-like peptide 1 (GLP-1) analog being developed by Eli Lilly for the treatment of type 2 diabetes mellitus (T2DM). **Dulaglutide consists of GLP-1(7-37) covalently linked to an Fc fragment of human IgG4, thereby protecting the GLP-1 moiety from inactivation by dipeptidyl peptidase 4.** In vitro and in vivo studies on T2DM models demonstrated glucose-dependent insulin secretion stimulation. Pharmacokinetic studies demonstrated a t1/2 in humans of up to 90 h, making dulaglutide an ideal candidate for once-weekly dosing. Clinical trials suggest that dulaglutide **reduces plasma glucose**, and has an insulinotropic effect increasing insulin and C-peptide levels. Two phase II clinical trials demonstrated a **dose-dependent reduction in glycated hemoglobin (HbA1c)** of up to 1.52% compared with placebo. **Side effects associated with dulaglutide administration were mainly gastrointestinal**. To date, there have been no reports on the formation of antibodies against dulaglutide, but, clearly, long-term data will be needed to asses this and other possible side effects. The results of several phase III clinical trials are awaited for clarification of the expected effects on HbA1c and body weight. **If dulaglutide possesses similar efficacy to other GLP-1 analogs, the once-weekly treatment will most likely be welcomed by patients with T2DM.**

Diabetes Obes Metab. 2011 May;13(5):418-25

The effects of LY2189265, a long-acting glucagon-like peptide-1 analogue, in a randomized, placebo-controlled, double-blind study of overweight/obese patients with type 2 diabetes: the EGO study.

Umpierrez GE, Blevins T, Rosenstock J, Cheng C, Anderson JH, Bastyr EJ 3rd; EGO Study Group.

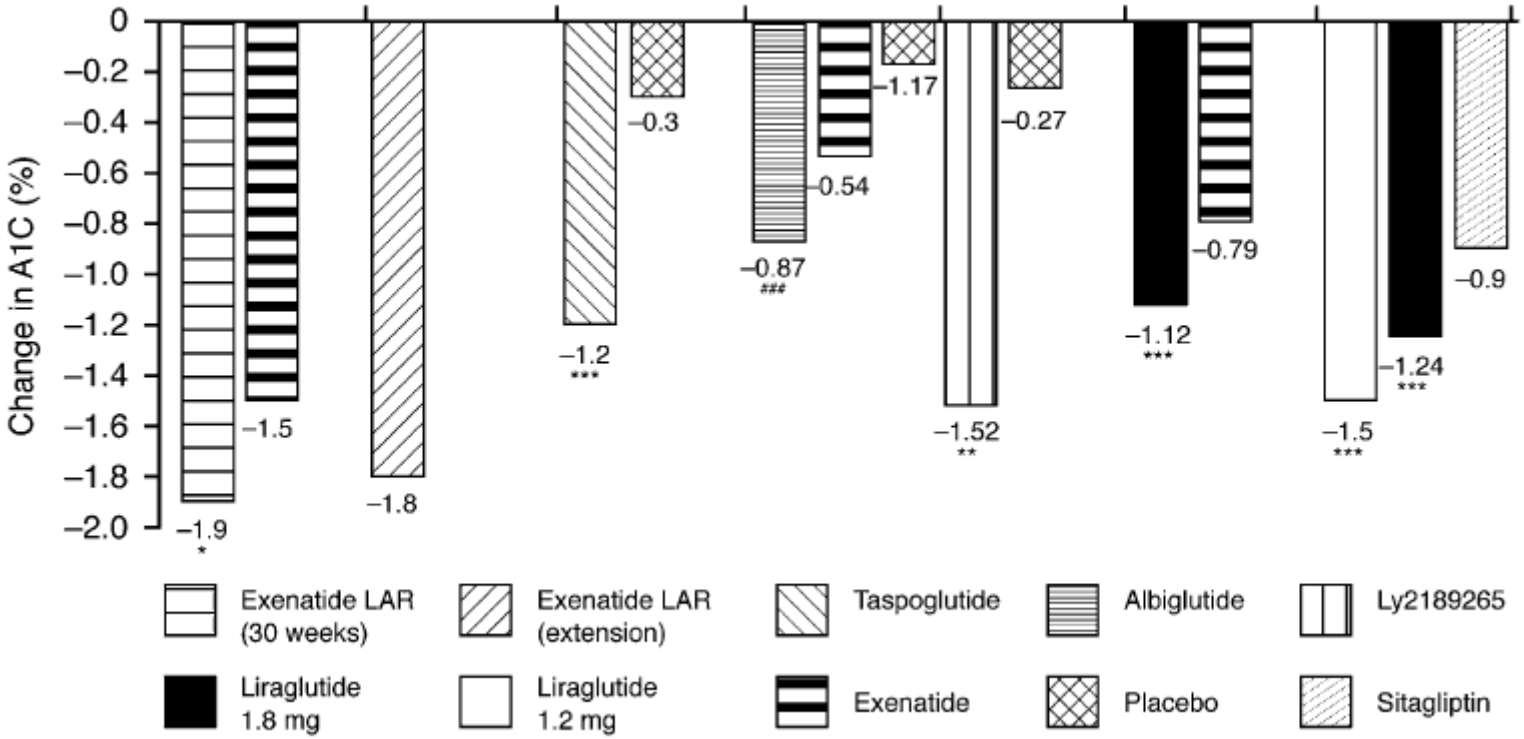
AIM: To evaluate the efficacy and tolerability of once-weekly LY2189265 (LY), a novel glucagon-like peptide-1 (GLP-1) IgG4-Fc fusion protein, in patients with type 2 diabetes failing oral antihyperglycaemic medications (OAMs).

METHODS: Placebo-controlled, double-blind study in 262 patients (mean age 57 ± 12 years; BMI 33.9 ± 4.1 kg/m(2); and glycosylated haemoglobin A1c (A1c) 8.24 ± 0.93%) receiving two OAMs. Patients were randomized to once-weekly subcutaneous injections of placebo or LY 0.5 mg for 4 weeks, then 1.0 mg for 12 weeks (LY 0.5/1.0); 1.0 mg for 16 weeks (LY 1.0/1.0); or 1.0 mg for 4 weeks, then 2.0 mg for 12 weeks (LY 1.0/2.0).

RESULTS: At week 16, A1c changes (least-squares mean ± standard error) were -0.24 ± 0.12, -1.38 ± 0.12, -1.32 ± 0.12 and -1.59 ± 0.12%, in the placebo, LY 0.5/1.0, LY 1.0/1.0 and LY 1.0/2.0 arms, respectively (all $p < 0.001$ vs. placebo). Both fasting ($p < 0.001$) and postprandial ($p < 0.05$) blood glucose decreased significantly compared to placebo at all LY doses. Weight loss was dose dependent and ranged from -1.34 ± 0.39 to -2.55 ± 0.40 kg at 16 weeks (all $p < 0.05$ vs. placebo). At the highest LY dosage, the most common adverse events were nausea (13.8%), diarrhoea (13.8%) and abdominal distension (13.8%). Hypoglycaemia was uncommon overall (≤0.8 episodes/patient/30 days) but more common with LY than placebo through the initial 4 weeks ($p < 0.05$). No differences in cardiovascular events or blood pressure were shown between treatments.

CONCLUSIONS: LY2189265, given to overweight/obese patients with type 2 diabetes for 16 weeks in combination with OAMs, was relatively **well tolerated and significantly reduced A1c, blood glucose and body weight.**

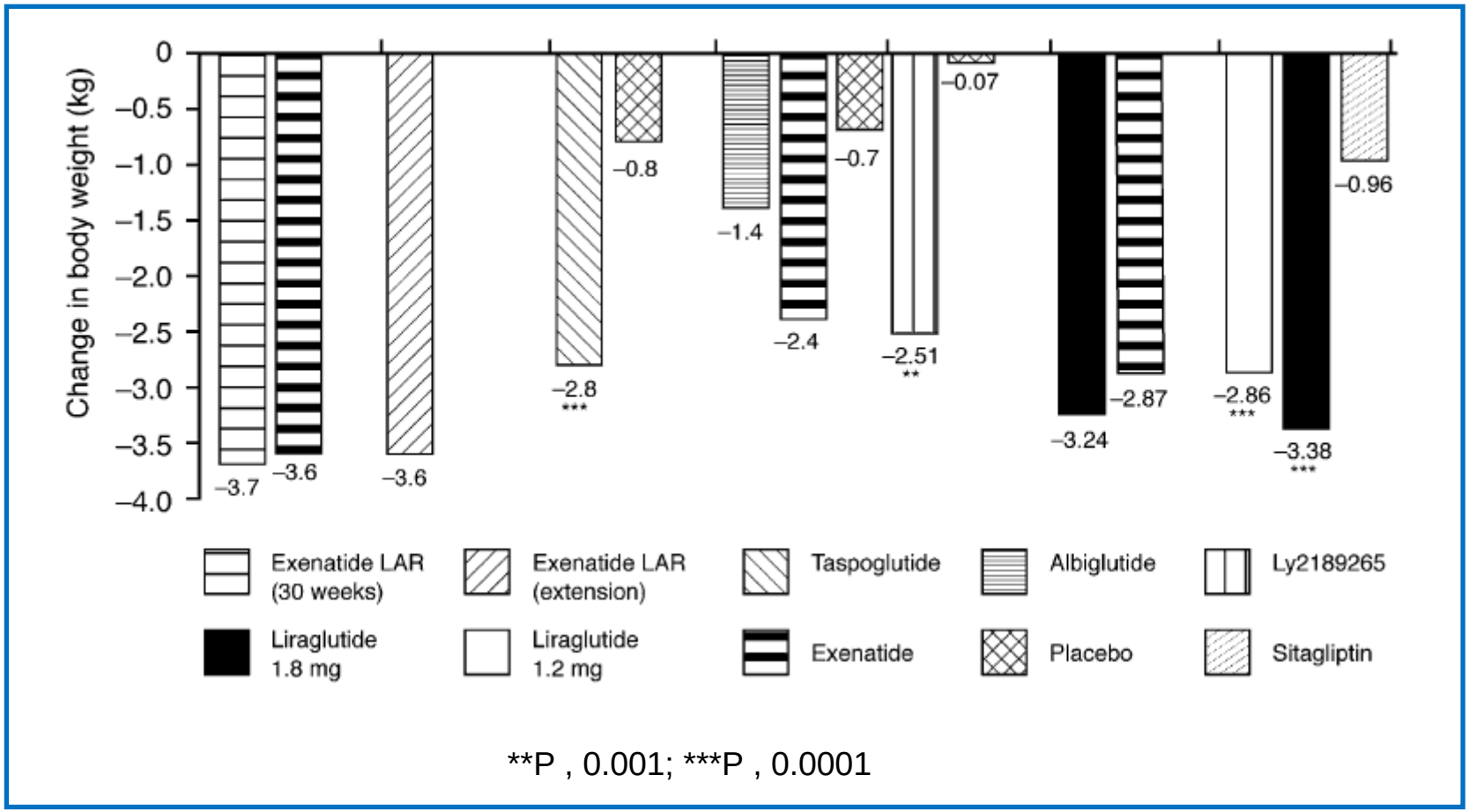
Change in A1C with long-acting GLP-1 receptor agonists across the clinical trials



*P , 0.01 vs. comparator; **P , 0.001; ***P , 0.0001; ###P , 0.0001 vs. placebo

Garber AJ, Diabetes Care 2011, 34 (suppl 2): S279-S284

Change in body weight with long-acting GLP-1 receptor agonists across the clinical trials



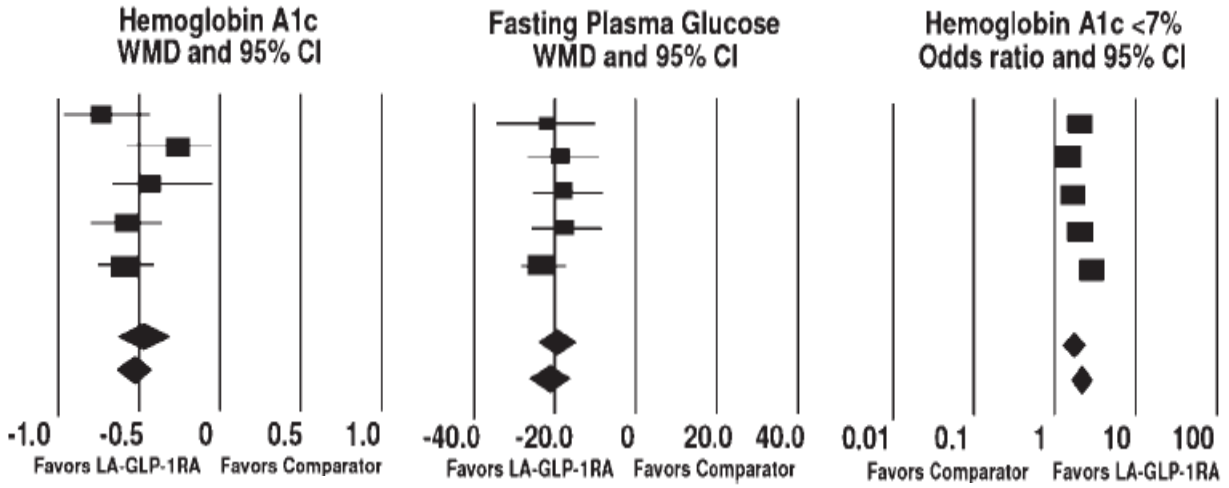
**P , 0.001; ***P , 0.0001

Garber AJ, Diabetes Care 2011, 34 (suppl 2): S279-S284

Efficacy and Safety of Long-Acting Glucagon-Like Peptide-1 Receptor Agonists Compared with Exenatide Twice Daily and Sitagliptin in Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis

Pinelli NR and Hurren KM, *Ann Pharmacother 2011;45:850-60.*

Study name	WMD	Lower limit	Upper limit
Blevins (2010)[26]	-0.70	-0.98	-0.42
Buse (2009)[27]	-0.33	-0.55	-0.11
Drucker (2008)[28]	-0.40	-0.68	-0.12
Bergenstal (2010)[30]	-0.60	-0.85	-0.35
Pratley (2010)[29]	-0.60	-0.78	-0.42
Vs. Exenatide BID	**-0.47**	**-0.69**	**-0.25**
Vs. Sitagliptin	**-0.60**	**-0.75**	**-0.45**



CONCLUSIONS: Compared with other incretin-based therapies, LA-GLP-1RAs produce **greater improvement in A1C and FPG**. They provide **lesser effect on PPG**, **similar reduction in body weight**, and result in a **potentially favorable adverse event profile compared with exenatide twice daily**.

Comparison of short-acting versus long-acting GLP-1 receptor agonists

Parameters	Short-acting GLP-1 receptor agonists	Long-acting GLP-1 receptor agonists
Compounds	Exenatide Lixisenatide	Albiglutide Dulaglutide Exenatide-LAR Liraglutide
Half-life	2–5 h	12 h–several days
Effects		
Fasting blood glucose levels	Modest reduction	Strong reduction
Postprandial hyperglycaemia	Strong reduction	Modest reduction
Fasting insulin secretion	Modest stimulation	Strong stimulation
Postprandial insulin secretion	Reduction	Modest stimulation
Glucagon secretion	Reduction	Reduction
Gastric emptying rate	Deceleration	No effect
Blood pressure	Reduction	Reduction
Heart rate	No effect or small increase (0–2 bpm)	Moderate increase (2–5 bpm)
Body weight reduction	1–5 kg	2–5 kg
Induction of nausea	20–50%, attenuates slowly (weeks to many months)	20–40%, attenuates quickly (~4–8 weeks)

Abbreviations: GLP-1, glucagon-like peptide 1; LAR, long-acting release.

CONCLUSIONE

The availability of GLP-1-based drugs with different pharmacokinetic properties, and the possibility of administering these compounds in various combinations, could increase our flexibility to provide individualized care to patients with type 2 diabetes mellitus.