
SID
fondata nel 1964
Società Italiana di Diabetologia
AMD
ASSOCIAZIONE MEDICI DIABETOLOGI
1974
CONGRESSO
SID-AMD
REGIONE
ABRUZZO-MOLISE
2020
GLP-1 RA: Similitudini e differenze tra le diverse molecole
WEBINAR
7 NOVEMBRE 2020
Fabrizio Febo MD, PhD
Specialista in Endocrinologia e malattie del metabolismo

Disclosure

Il Dott. Fabrizio Febo dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

Alfasigma Astrazeneca Boeringer Ingheleim Bruno Eli Lilly Mundipharma

MSD Novonordisk Sanofi

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

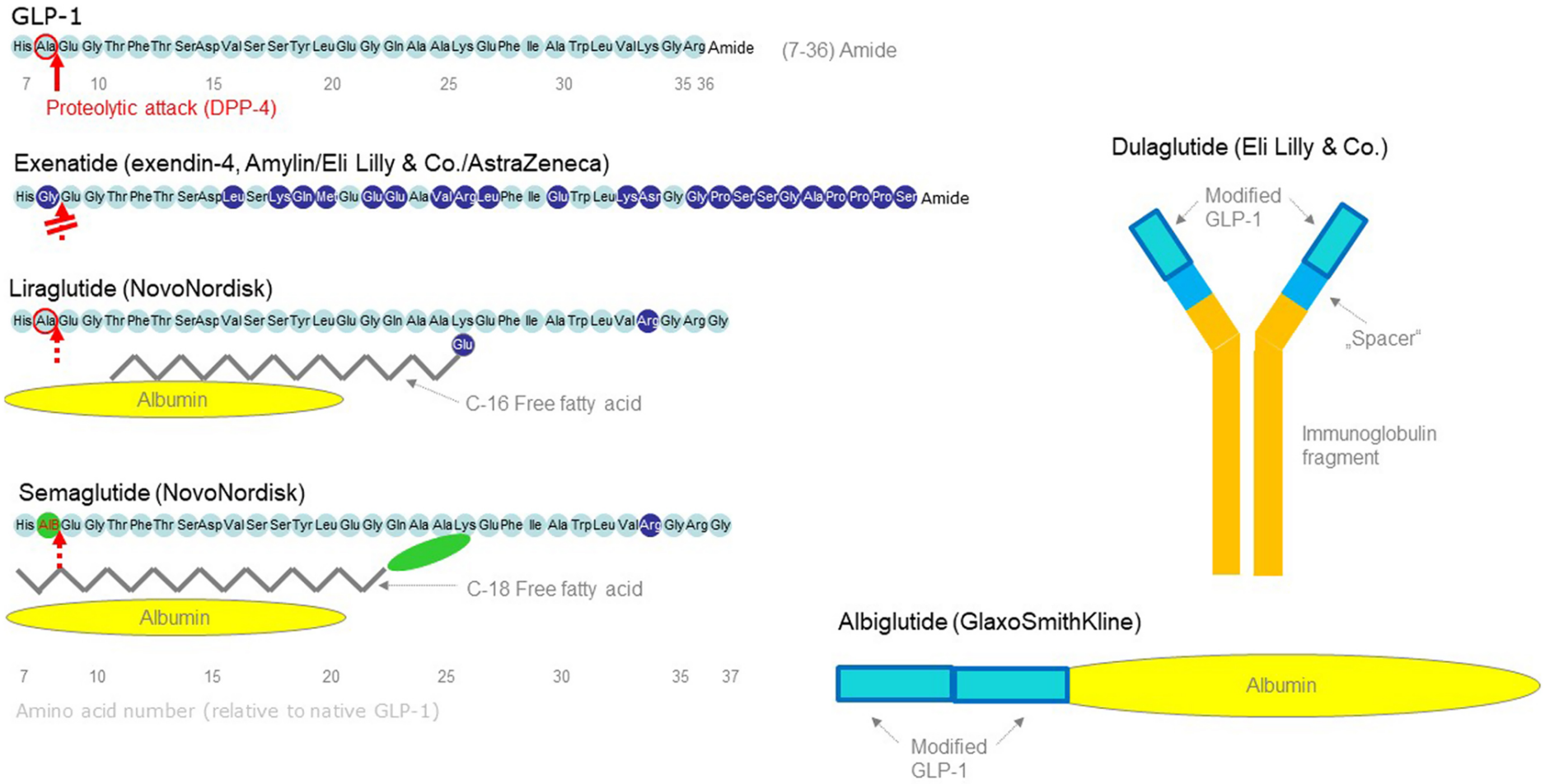
ECM al tempo del COVID

GLP-1 RA: Similitudini e differenze tra le diverse molecole

- Questione di chimica…
- …Efficacia e Sicurezza Clinica…
- …Sicurezza e riduzione del rischio CV…
- …aderenza al trattamento…
- …la nuova era dei GLP-1

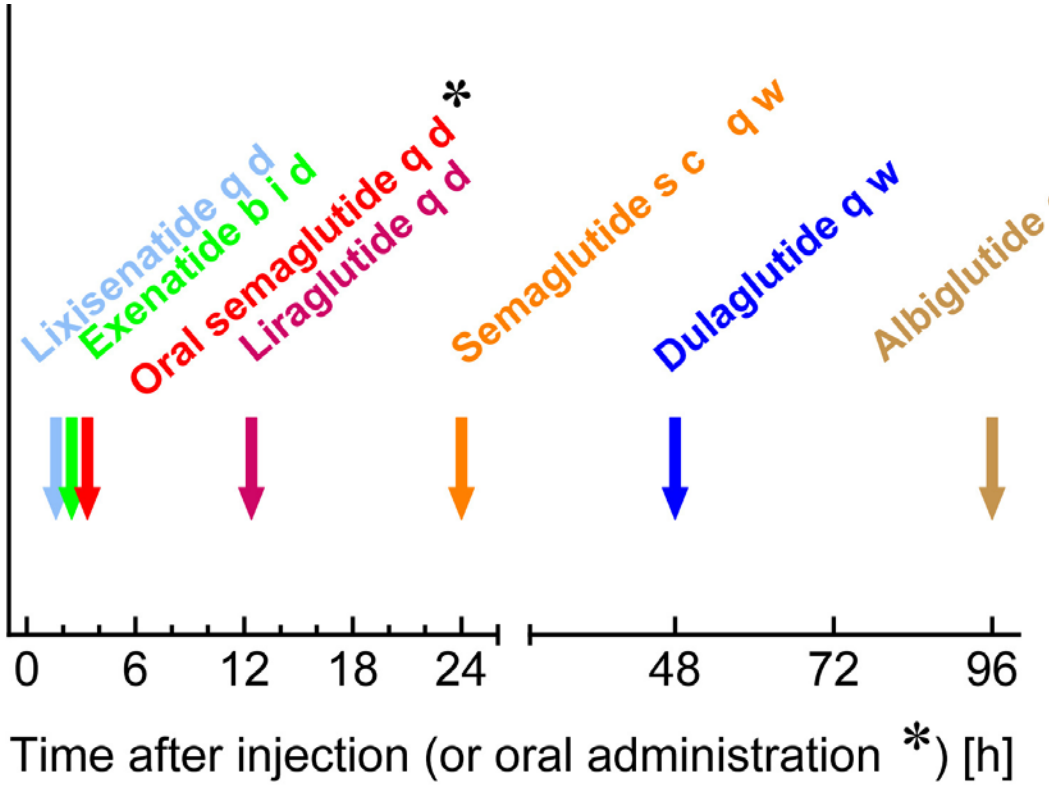

SAME
BUT DIFFERENT

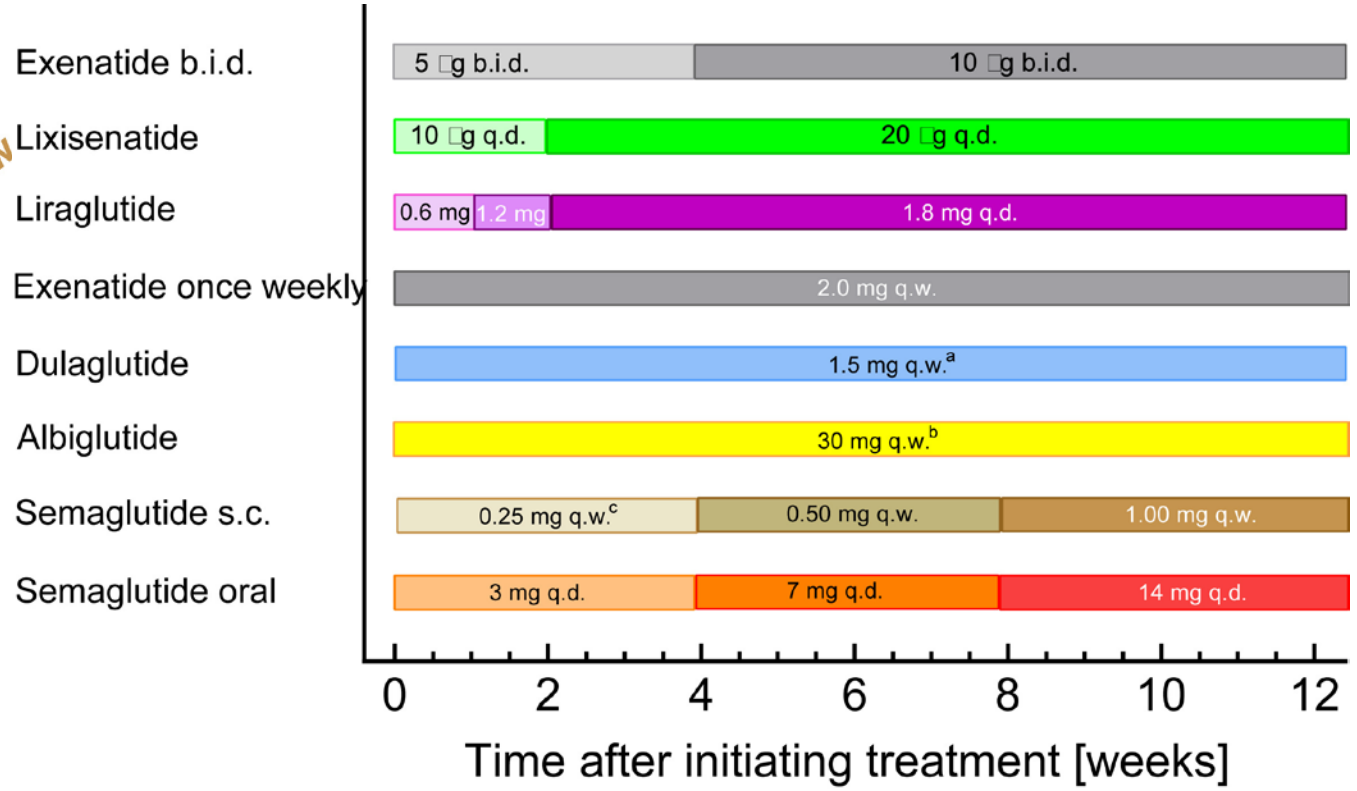
GLP-1 RAs -Molecular Structure



Nauk & Meier *European Journal of Endocrinology* (2019) **181**, R211–R234

GLP-1 RAs – Doses and Titration

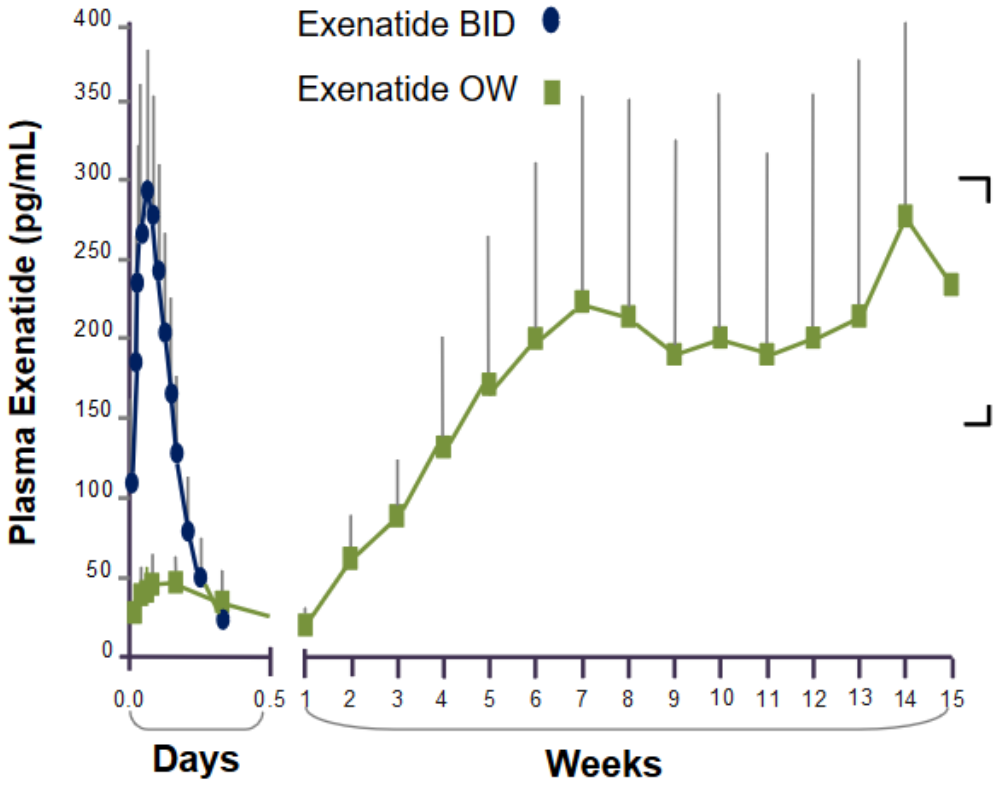




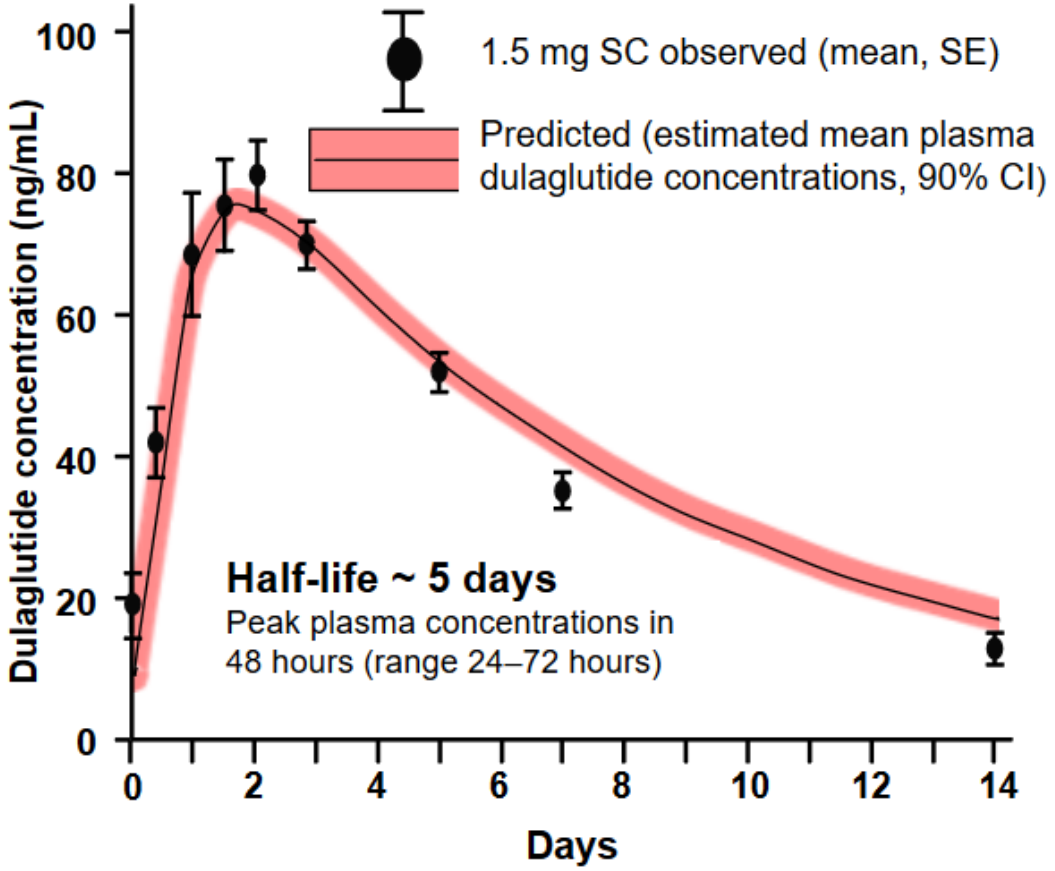
Nauk Molecular Metabolism 2020

Pharmacokinetics of Exenatide BID/OW and Dulaglutide

Pharmacokinetics of short (twice-daily, BID) or long (once-weekly, OW) acting exenatide[1,2]



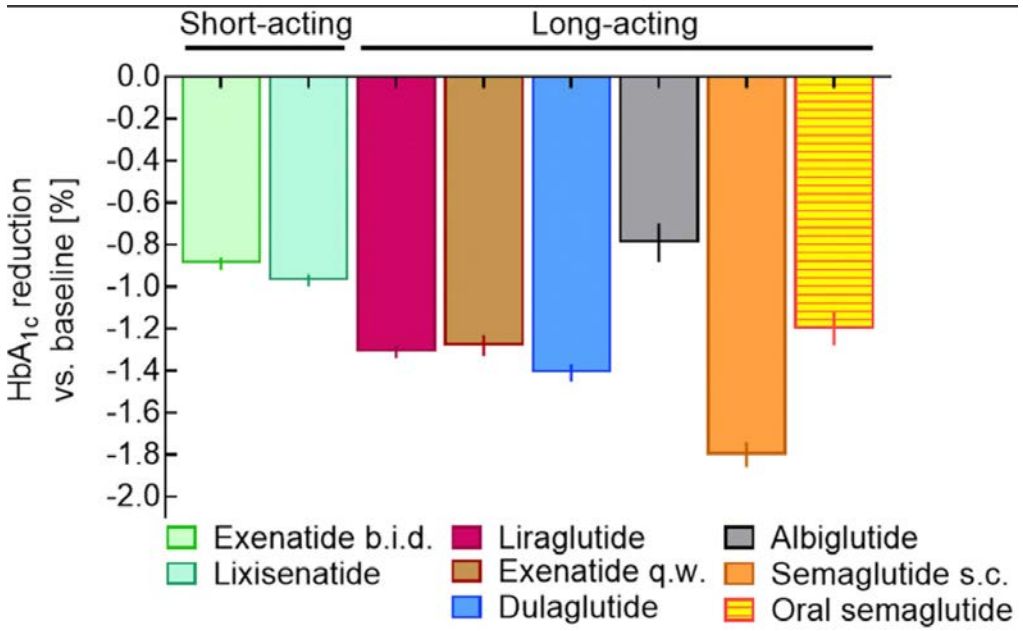
Dulaglutide 1.5 mg once-weekly SC concentration–time profile[3]

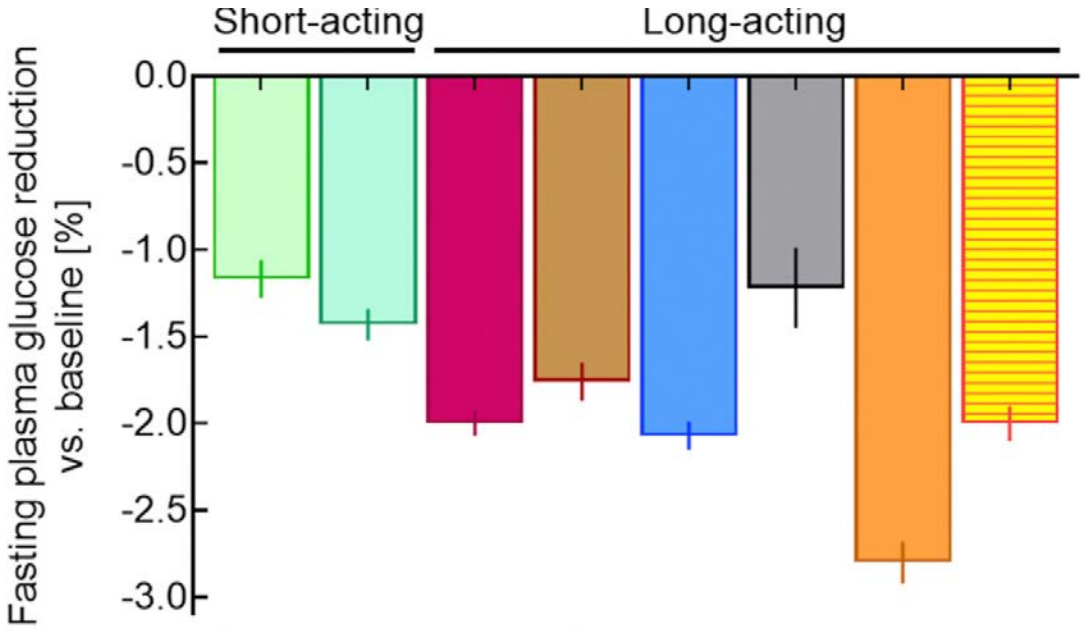


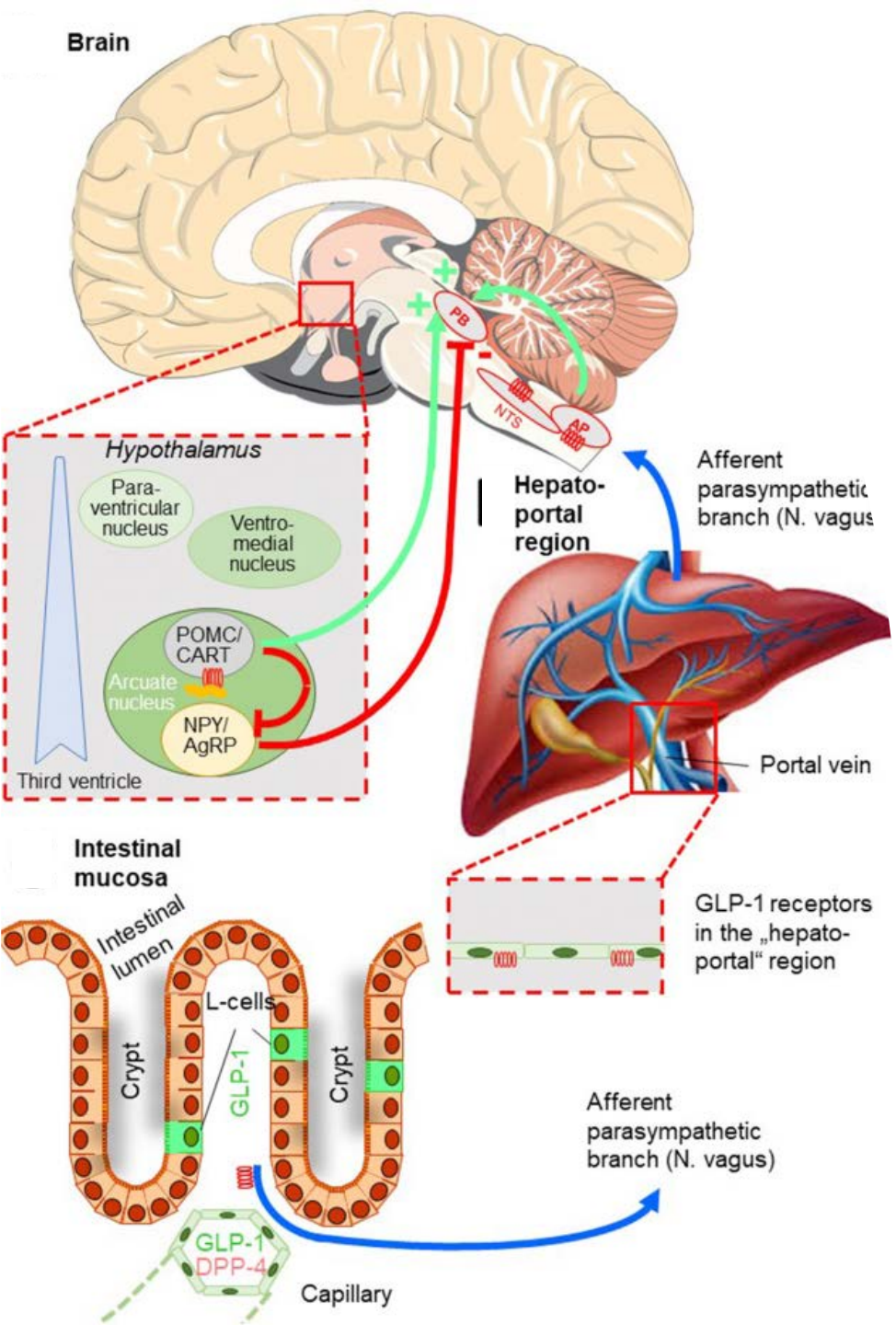
BID, twice daily; CI, confidence interval; OW, once weekly; SC, subcutaneous; SE, standard errar

[1]Kim D, et al. *Diabetes Care* 2007;30 1487- 1493; [2]Fineman M, et al. *Clin Pharmacokinet* 2011;50 65-74; [3]de la Pena A, et al. 50th EASD Annual Meeting, Vienna, Austria, 15-19 September 2014 [PS 066 Novel therapies; P-857]

Glucose lowering efficacy



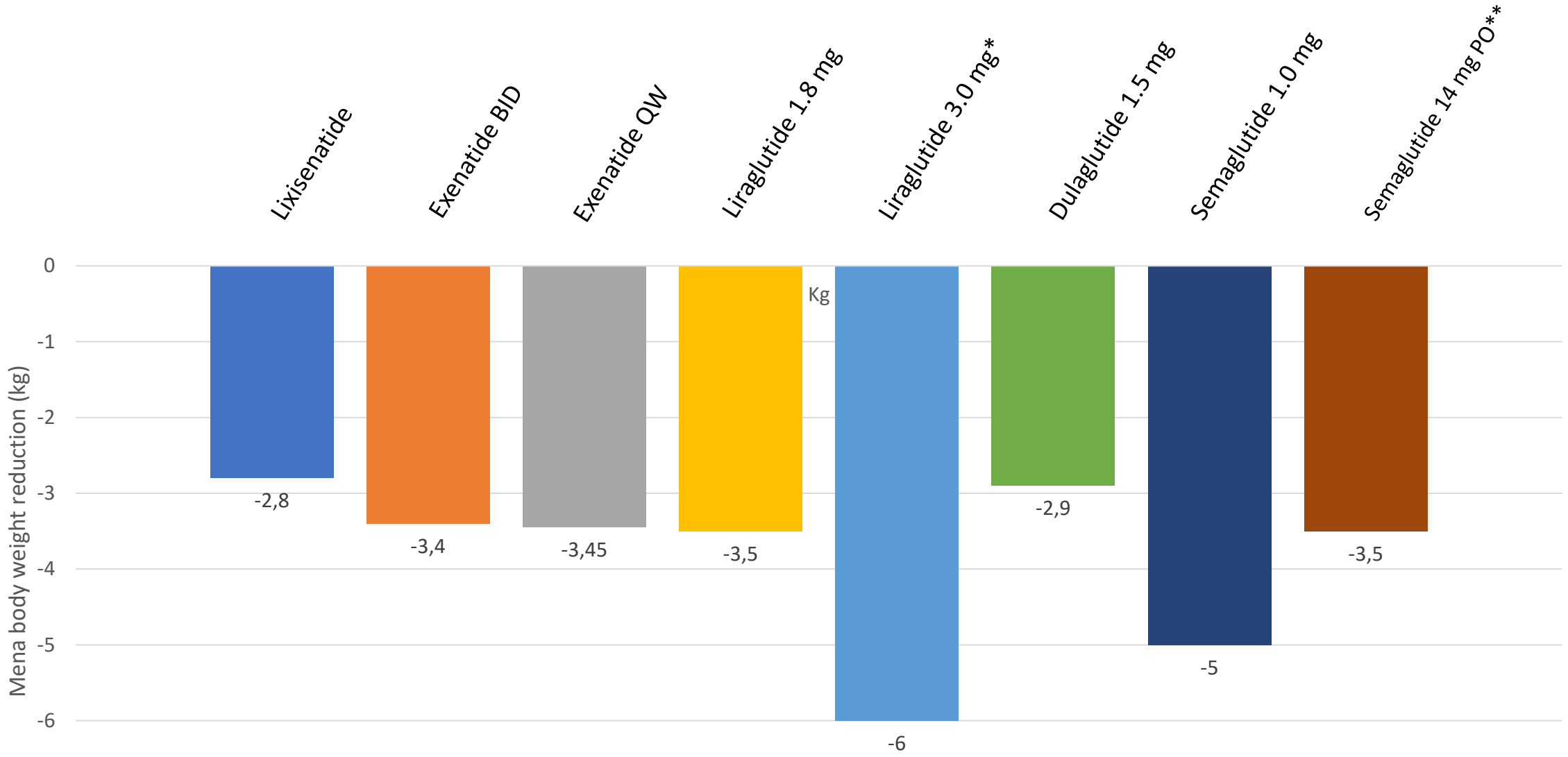




GLP-1 Body weight and food intake regulation

- Reduces Appetite
- Prospective Food Consumption
- Increases Satiety And Feeling Of Abdominal Fullness,
- Limits Caloric Intake In “Ad Libitum“ Feeding

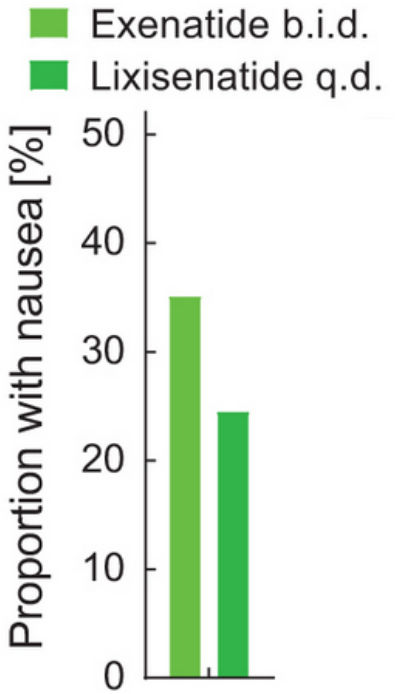
MEAN BODY WEIGHT REDUCTION



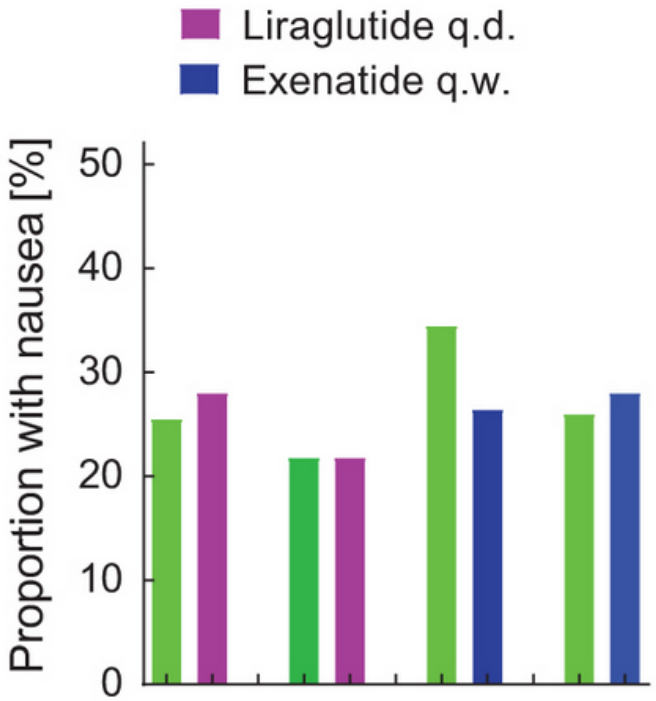
Brown et Al, Ob Rev 2019

*for obesity use
** not availabe in EU

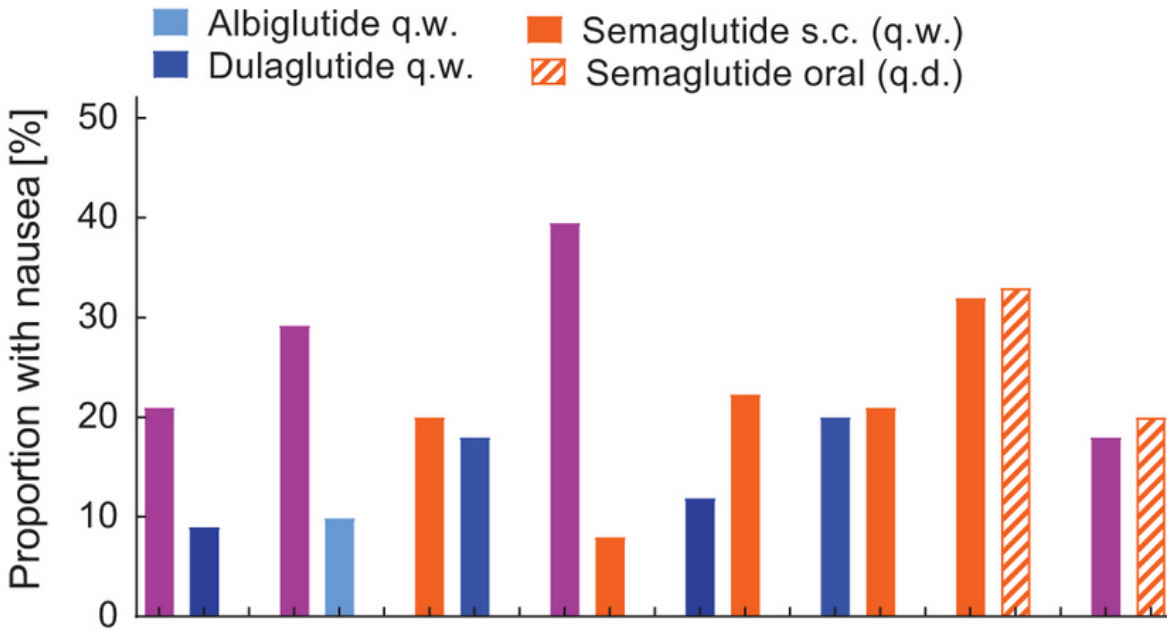
Tollerability



Short vs short

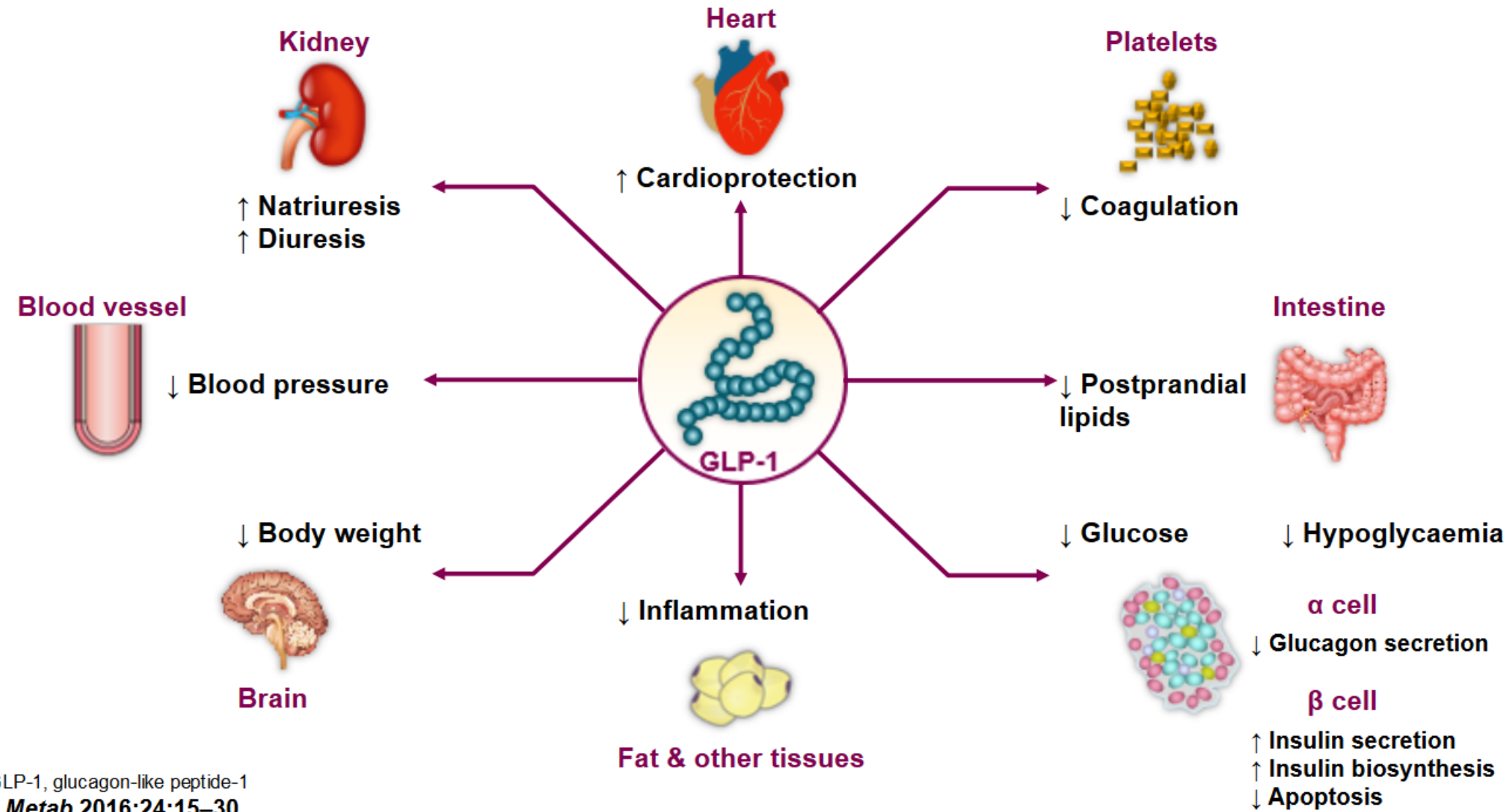


Short vs long



Long vs Long

GLP-1 Effects on CV Risk through Direct and Indirect Actions in Multiple Organs



CV, cardiovascular; GLP-1, glucagon-like peptide-1

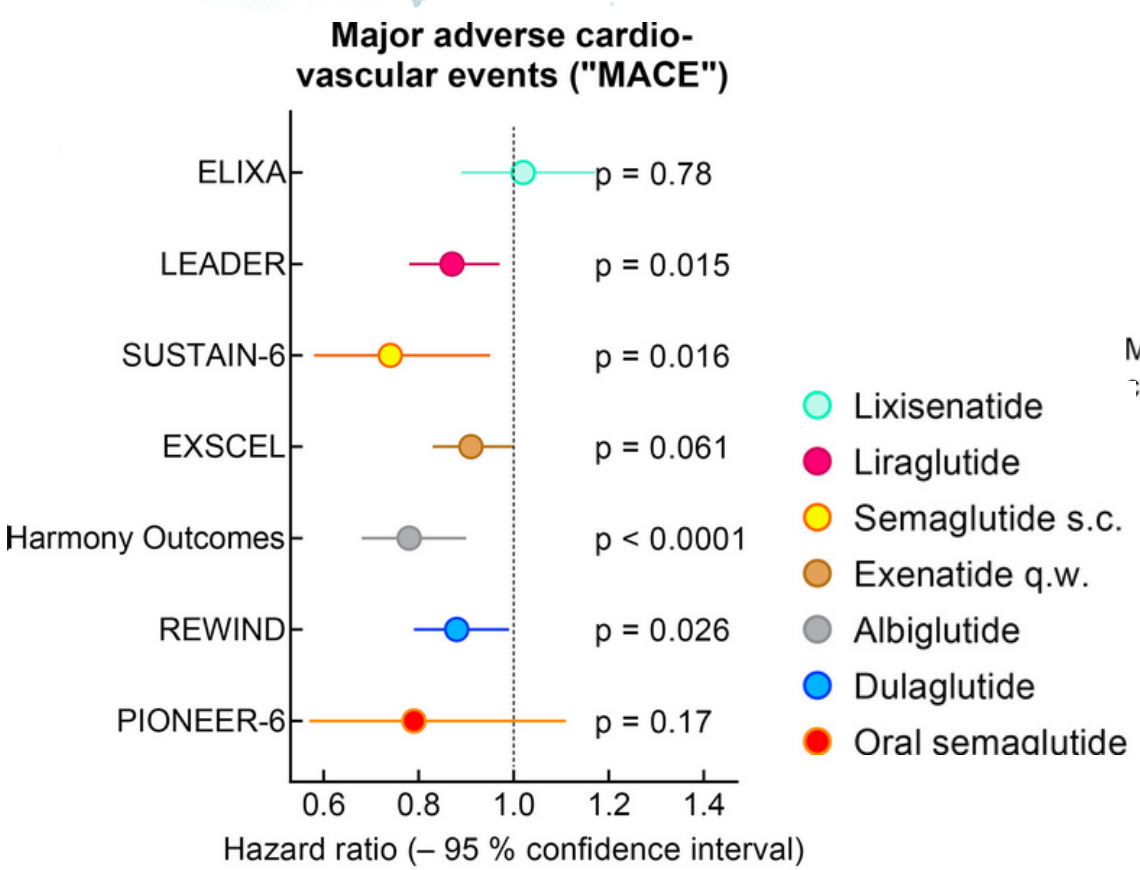
Drucker DJ. *Cell Metab* 2016;24:15–30

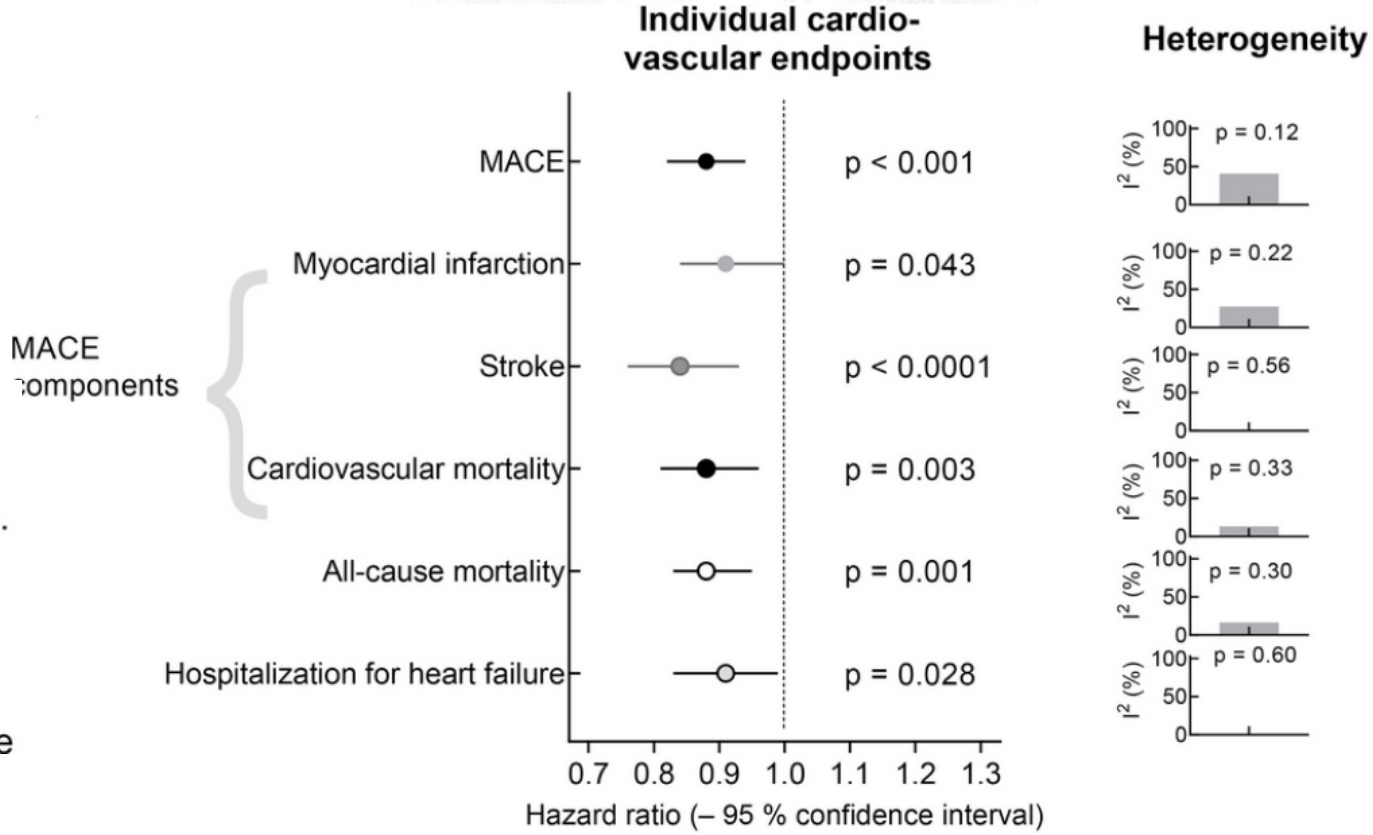

RWE?
CVOT?
SHORT or LONG ACTING?
HIGH or LOW RISK?
PRAGMATIC?
NON INFERIORITY or SUPERIORITY?
MACE 3? 4? 5?


CVOTs:
TRICK
OR
TREATMENT?

Adapted and modified from Kristensen, 2019 – Lancet Diab Endo

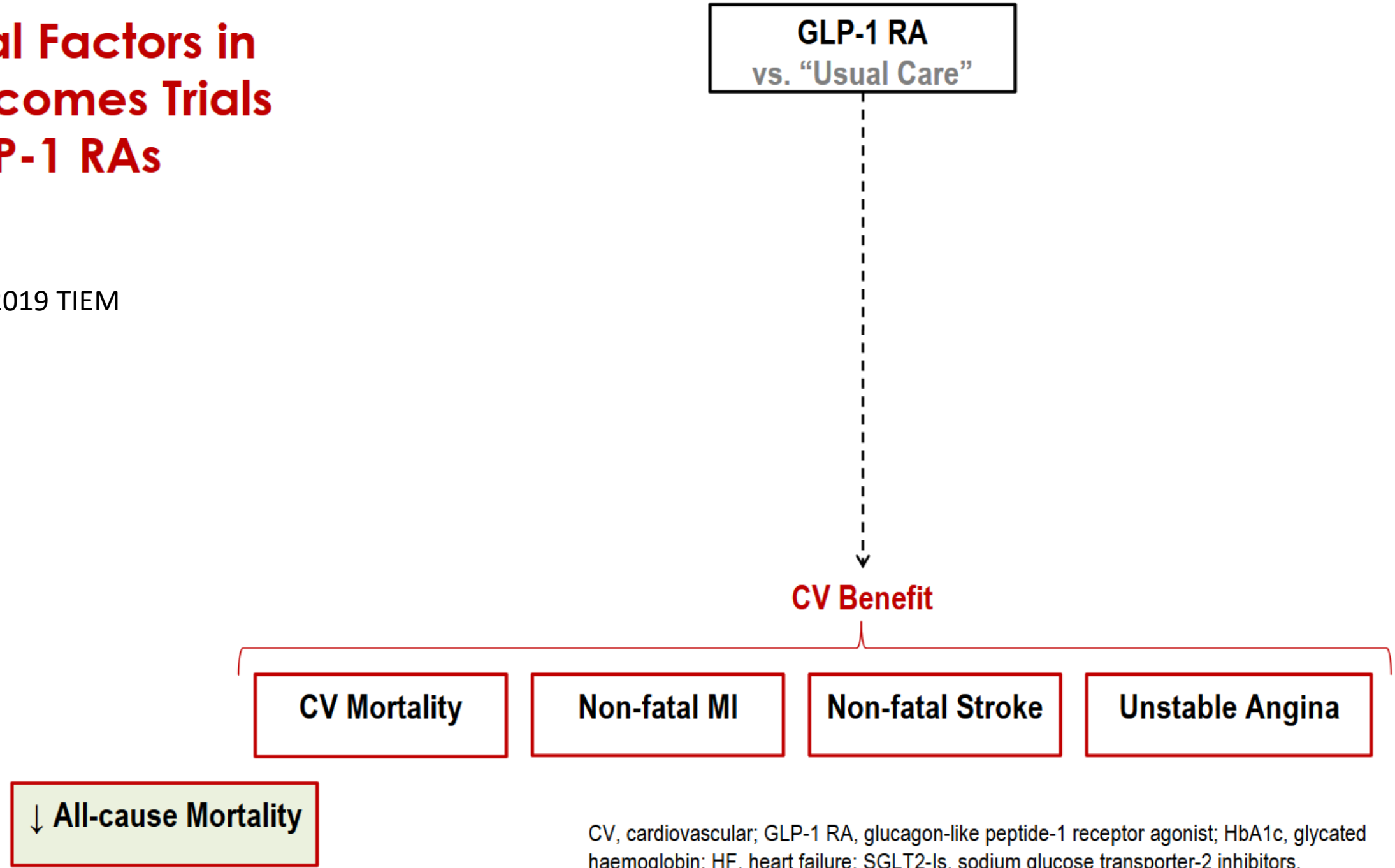
CVOTs RESULTS





Potential Factors in CV Outcomes Trials with GLP-1 RAs

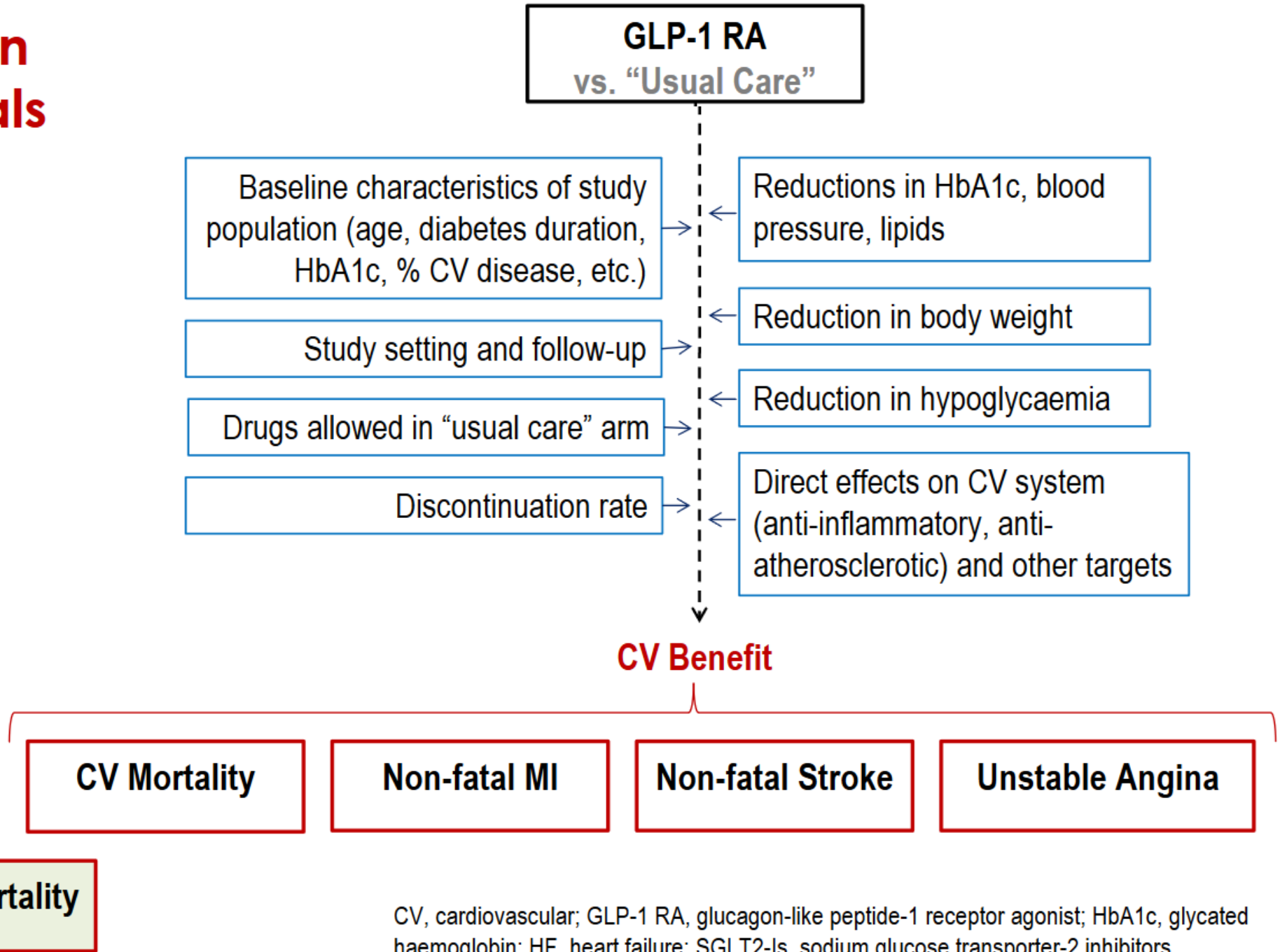
Caruso et Al, 2019 TIEM



CV, cardiovascular; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; HF, heart failure; SGLT2-Is, sodium glucose transporter-2 inhibitors.

Potential Factors in CV Outcomes Trials with GLP-1 RAs

Caruso et Al, 2019 TIEM

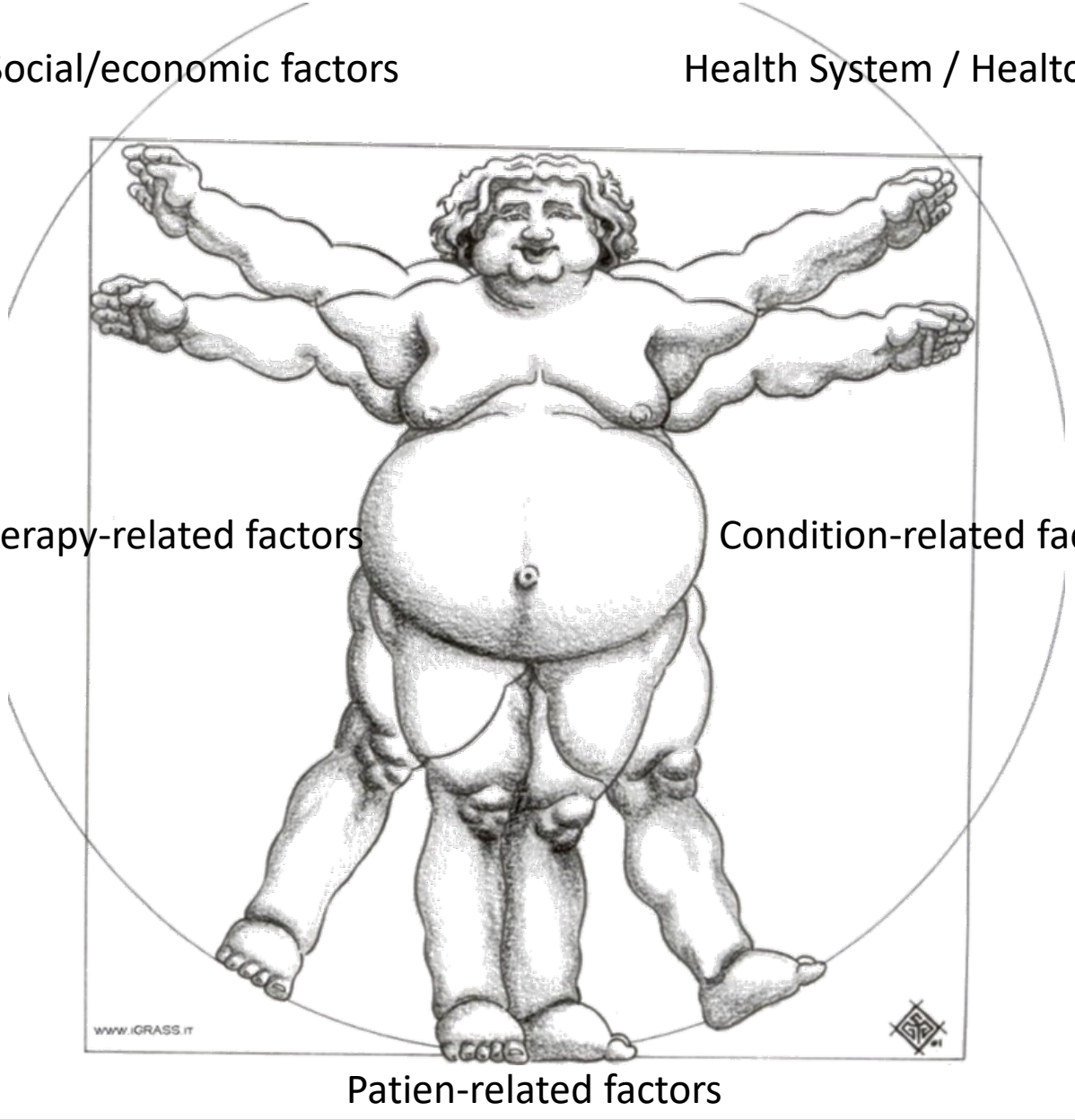


CV, cardiovascular; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; HF, heart failure; SGLT2-Is, sodium glucose transporter-2 inhibitors.

FIND THE DIFFERENCES…

Social/economic factors

Health System / Healtcare Team Factors



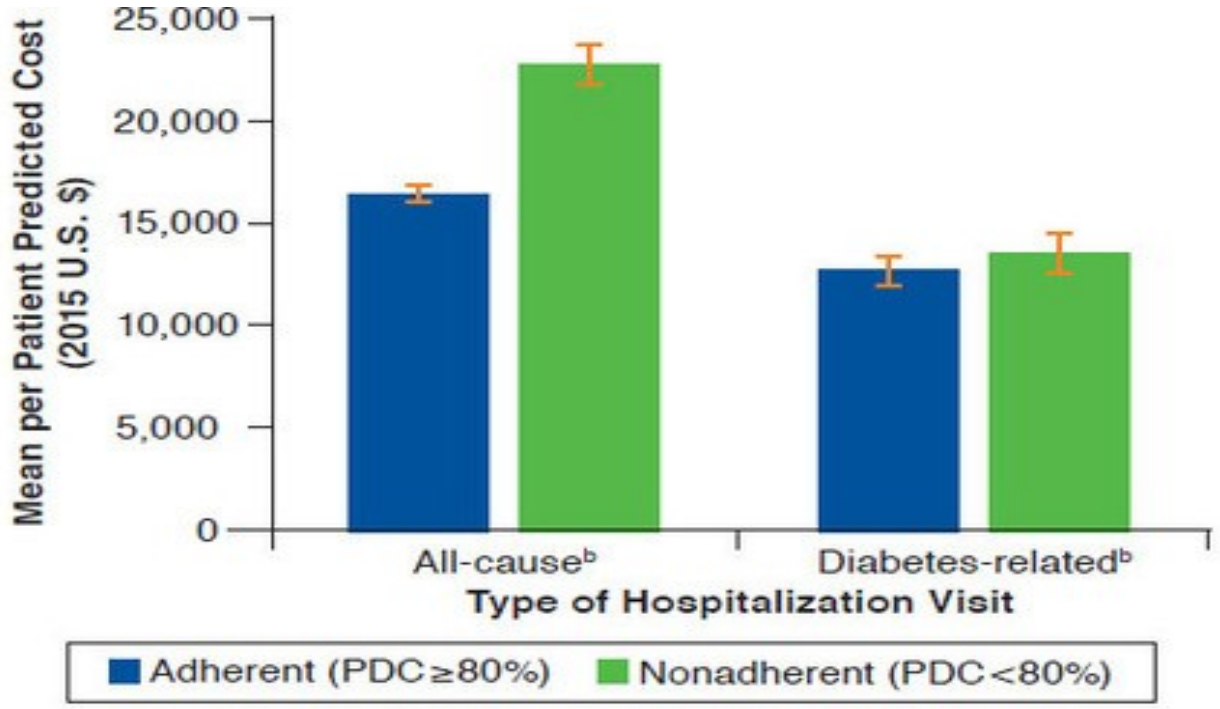
Therapy-related factors

Condition-related factors

Patien-related factors

CLINICAL ADHERENCE

Association of Medication Adherence with Hospital Utilization and Costs Among Elderly with Diabetes Enrolled in a State Pharmaceutical Assistance Program



	All-Cause (n = 1,907)	Diabetes-Related (n = 708)
Adherent, mean (95% CI)	$16,374 ($16,176-$16,571)	$12,659 ($12,348-$12,970)
Nonadherent, mean (95% CI)	$22,697 ($22,220-$23,173)	$13,515 ($13,060-$13,969)

[a]*Predicted costs estimates and corresponding 95% CIs based on generalized linear models, and corresponding P values based on paired t-tests.*

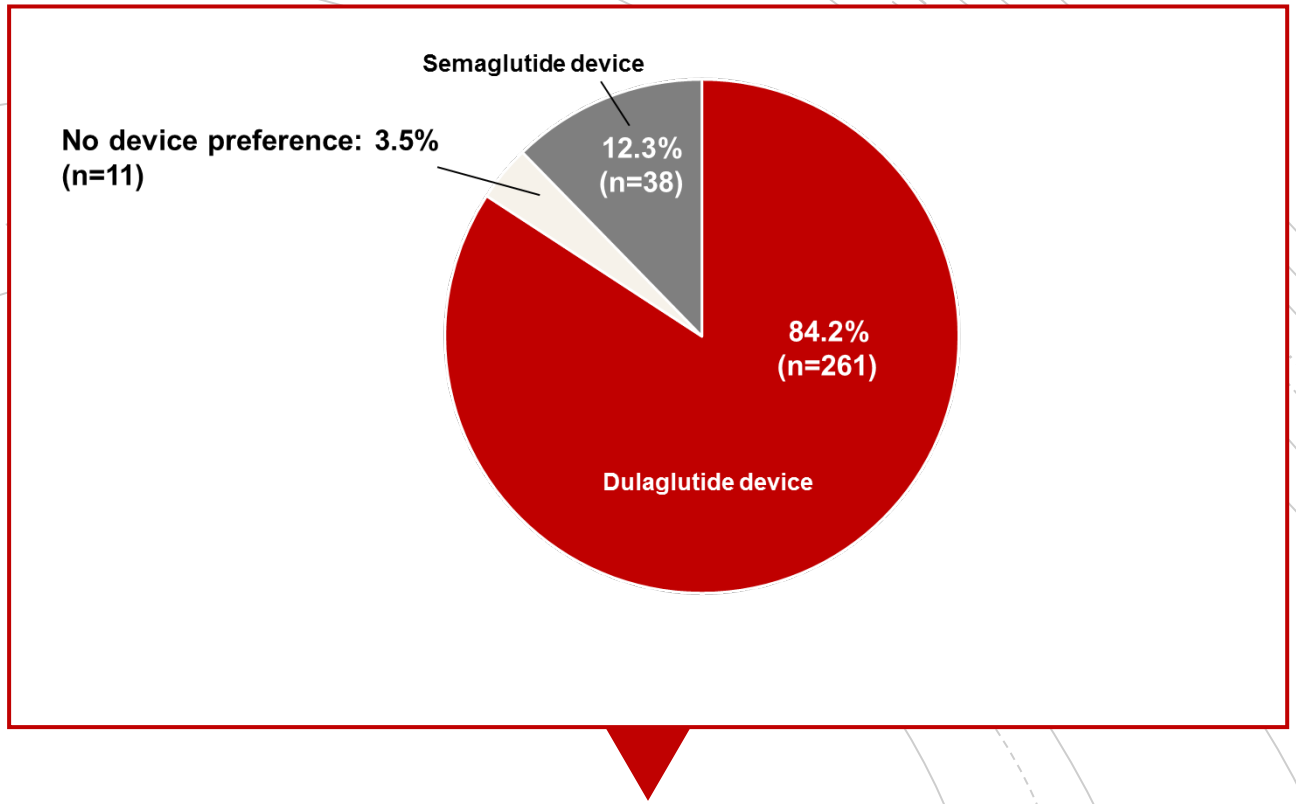
[b]*P* < 0.01

Medication nonadherence was associated with significantly greater

- all-cause ($22,670 vs. $16,383; $P < 0.0001$)
- diabetes-related ($13,518 vs. $12,634; $P = 0.0003$)

hospitalization costs.

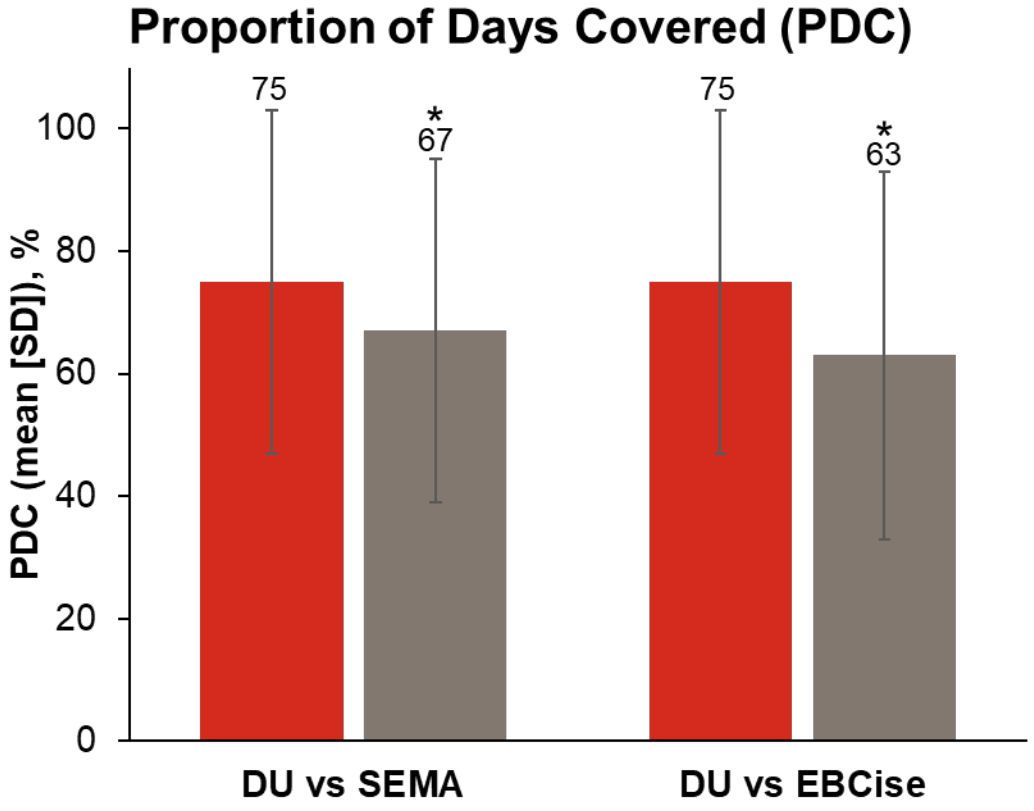
Pednekar P et Al, J Manag Care,2020

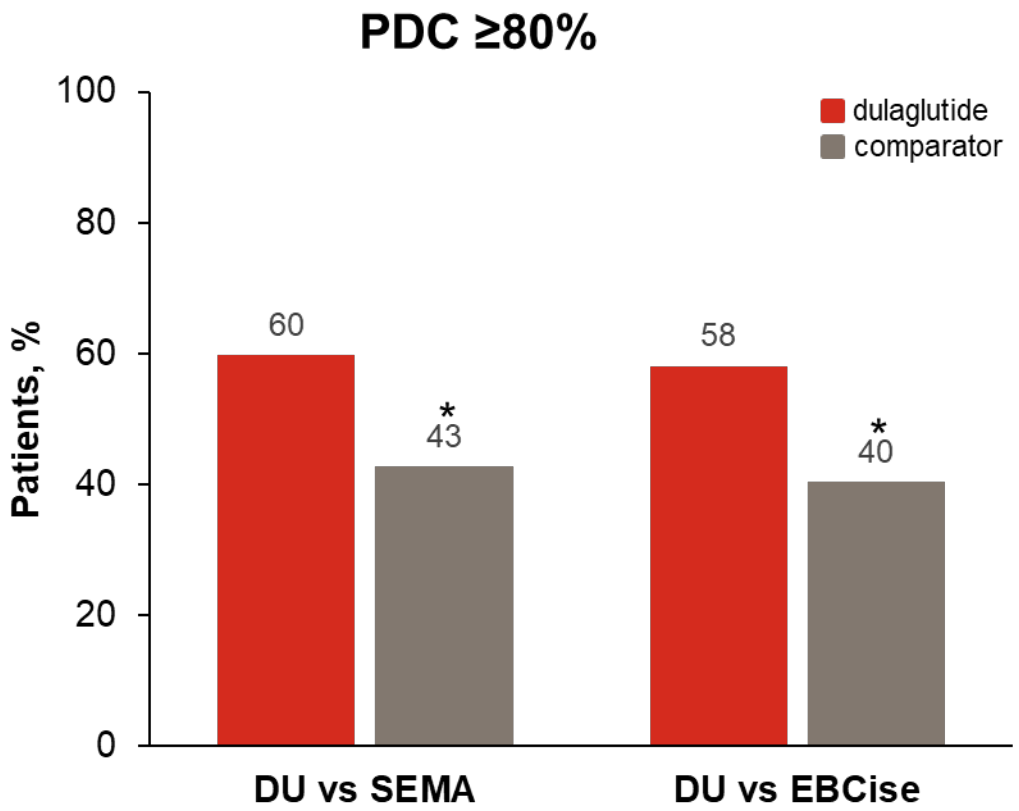


“Overall, which device do you prefer?”

Primary Outcome: Global Preference Item (N=310)

DULA vs SEMA vs EXE BCISE





*p<0.001 vs dulaglutide from t-test (continuous) or chi-square(categorical). Adherent patients were those with PDC ≥80%. Abbreviations: DU = dulaglutide; EBCise = exenatide BCise; PDC = proportion of days covered; SD = standard deviation; SEMA = semaglutide

Similarities and Differences within the GLP-1 RAsClass

Similarities

- Significant glycaemic improvement
- Low hypoglycaemia risk, except in combination with SU or insulin
- Weight reduction, usually dose-dependent and molecule-related
- Gastrointestinal side effects
- Potential to enhance beta-cell survival
- Cardiovascular protection
- Potential to counteract neurodegeneration

Differences

- Homology to human GLP-1 and immunogenicity
- Onset of action
- Effects on gastric emptying
- Fasting glucose and post-prandial glucose reduction
- Differences in metabolism and elimination (use in CKD)
- Potential for kidney protection
- CV protection
- Frequency of administratio,ndose titration, devices/pens, need for reconstitution adherence

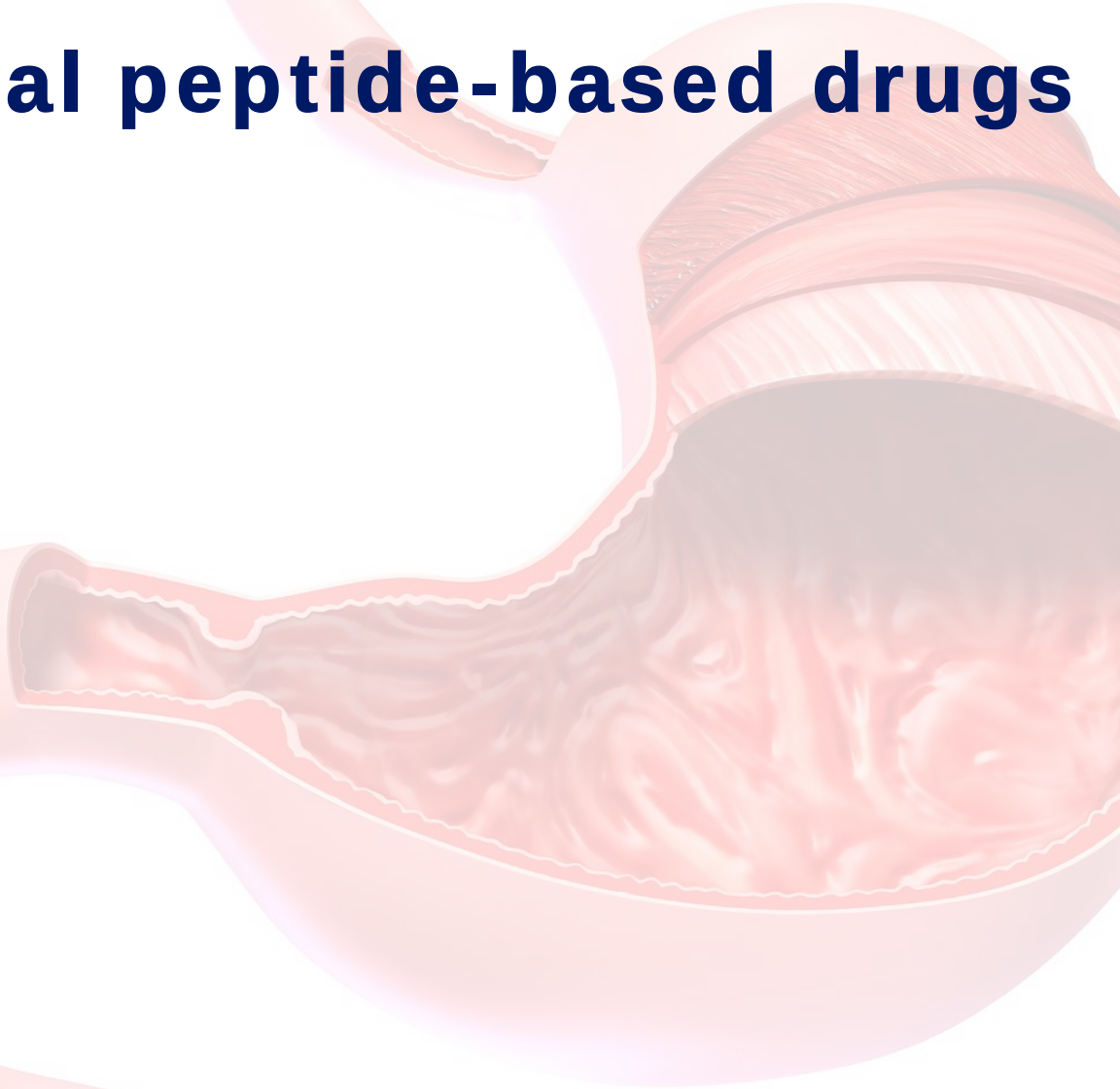
THE FUTURE


STEVEN SPIELBERG PRESENTS
BACK TO THE FUTURE
PG
A ROBERT ZEMECKIS FILM
OUTATIME

ORAL GLP-1

Absorption challenges of oral peptide-based drugs

- Degradation in the stomach
  - Low pH
  - Proteolytic enzymes
- Limited permeability across the gastrointestinal epithelium
- GLP-1RAs administered alone have very low oral bioavailability (<0.01%)



GLP-1RA, glucagon-like peptide-1 receptor agonist.

Renukuntla et al. *Int J Pharm*. 2013, Buckley ST et al. *Sci Transl Med* 2018;10:eaar7047.doi:10.1126/scitranslmed.aar7047.

Oral semaglutide | Tablet co-formulation with SNAC

Sodium **N**-(8-(2-hydroxybenzoyl) **A**mino) **C**aprylate (SNAC)

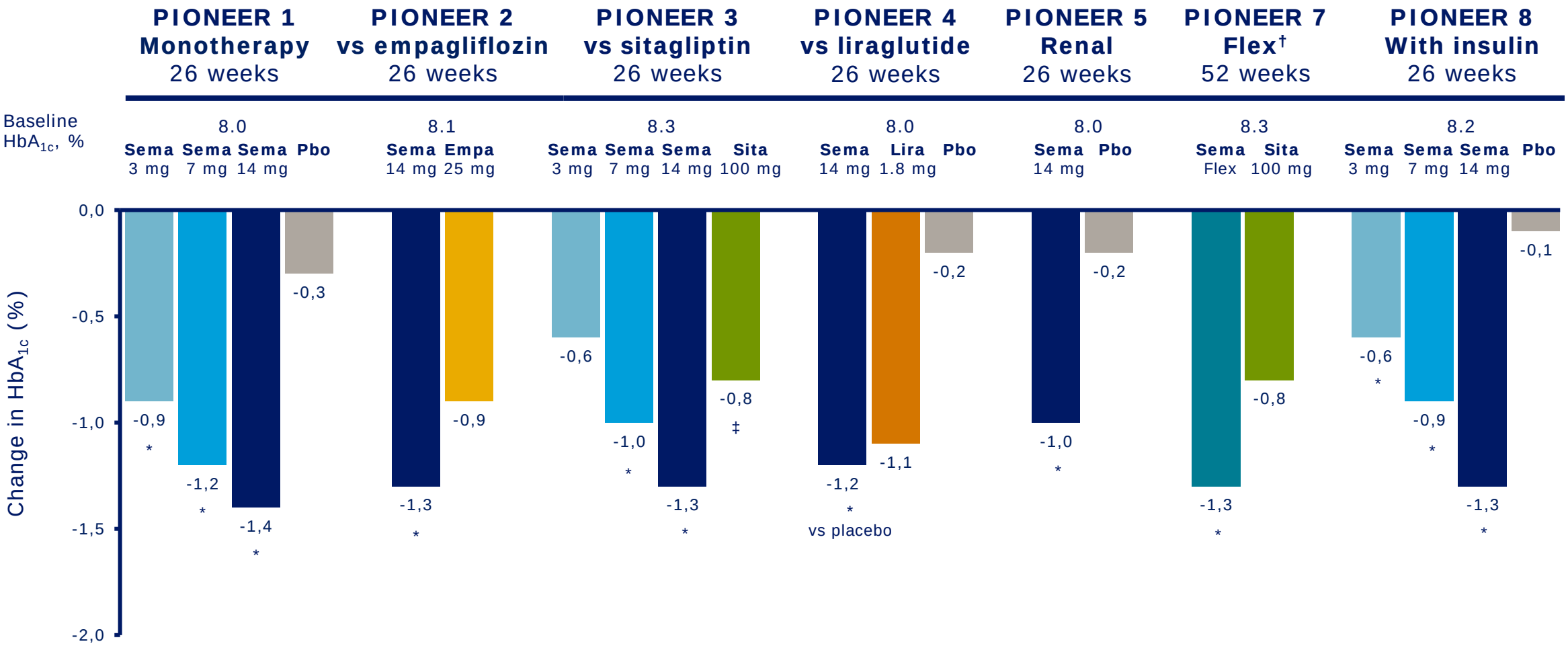
- Co-formulation of semaglutide with an absorption enhancer is necessary to achieve adequate bioavailability of oral administration[1]
- The absorption enhancer, SNAC, is a small fatty acid derivative that promotes absorption across the gastric epithelium[1,2]
- Oral semaglutide is co-formulated with 300 mg SNAC[1,2]

SNAC, Sodium N-(8-(2-hydroxybenzoyl) amino) caprylate.

1. Buckley ST et al. *Sci Transl Med* 2018;10:eaar7047.doi:10.1126/scitranslmed.aar7047; 2. Bækdal et al. Oral presentation OR–147, EASD 2017.

PIONEER 1, 2, 3, 4, 5, 7 and 8

CHANGE IN HbA_{1c} – TREATMENT POLICY ESTIMAND – PRIMARY ENDPOINT



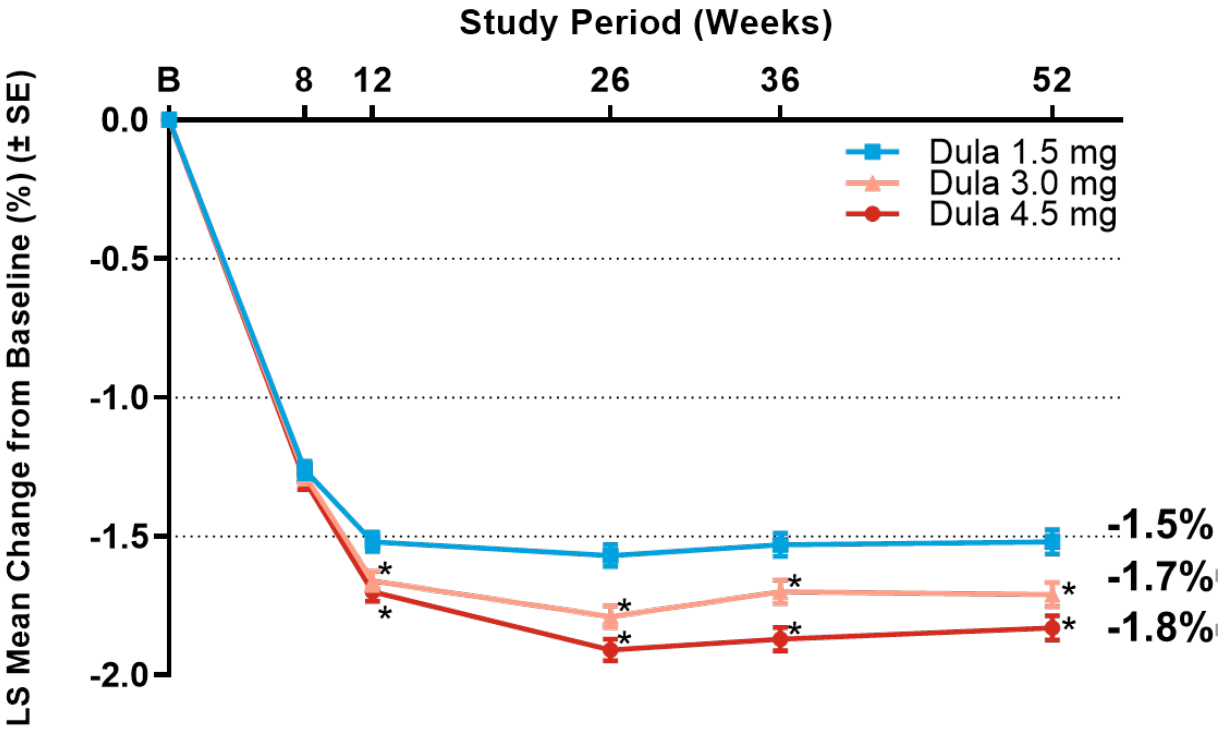
*Statistically significantly greater compared with placebo or active comparator. †Primary endpoint in PIONEER 7, subjects achieving HbA_{1c} <7.0%.
‡Statistically significantly in favor of sitagliptin 100 mg compared with oral semaglutide 3 mg. Flex, flexible; Empa, empagliflozin; Lira, liraglutide; Pbo, placebo; Sema, semaglutide; Sita, sitagliptin.

Aroda VR et al. *Diabetes Care* 2019. doi.org/10.2337/dc19-0749; Montanya E, et al. Oral presentation 54-OR. ADA 79th Annual Scientific Sessions. June 08, 2019;
Rosenstock J et al. *JAMA* 2019;321:1–15; Pratley R, et al. *Lancet* 2019. doi: 10.1016/S0140-6736(19)31271-1; Mosenzon O, et al. *Lancet Diabetes Endocrinol* 2019. doi: 10.1016/S2213-8587(19)30192-5;
Husain M, et al. *N Engl J Med* 2019. doi: 10.1056/NEJMoa1901118; Pieber TR, et al. Lancet Diabetes Endocrinol 2019. doi: 10.1016/S2213-8587(19)30194-9;
Zinman B, et al. Poster 985-P. ADA 79th Annual Scientific Sessions. June 10, 2019.

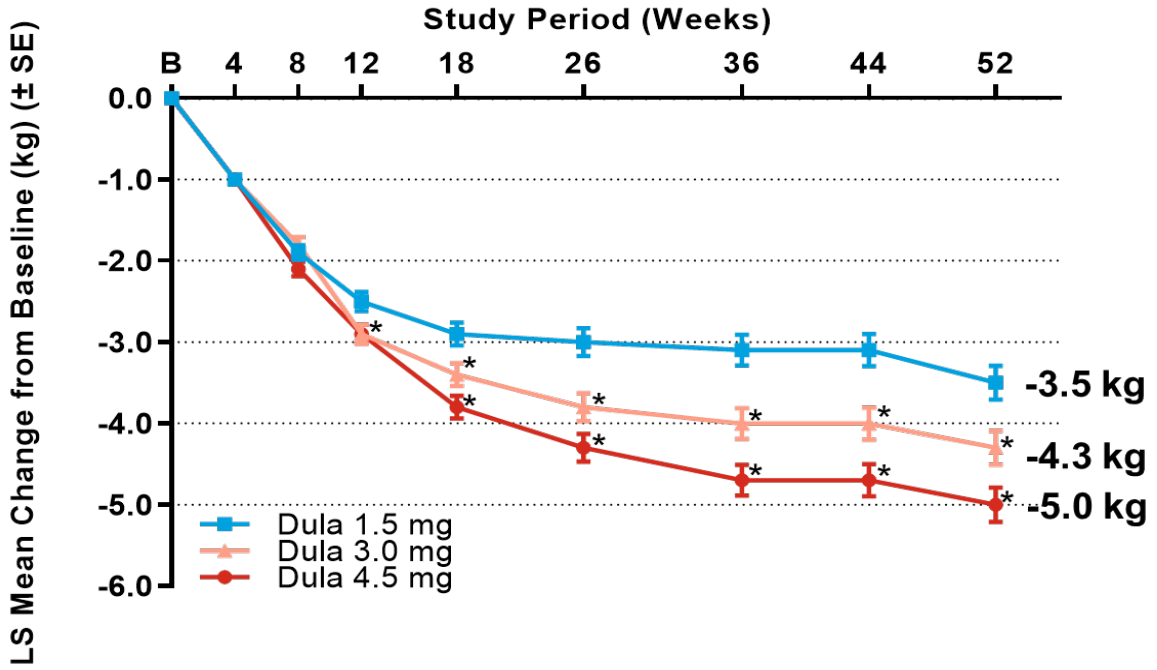
HIGHER DOSES

AWARD-11 CHANGE IN A1C & BODY WEIGHT THROUGH 52 WEEKS

Baseline A1C = 8.6%



Baseline body weight = 95.9 kg



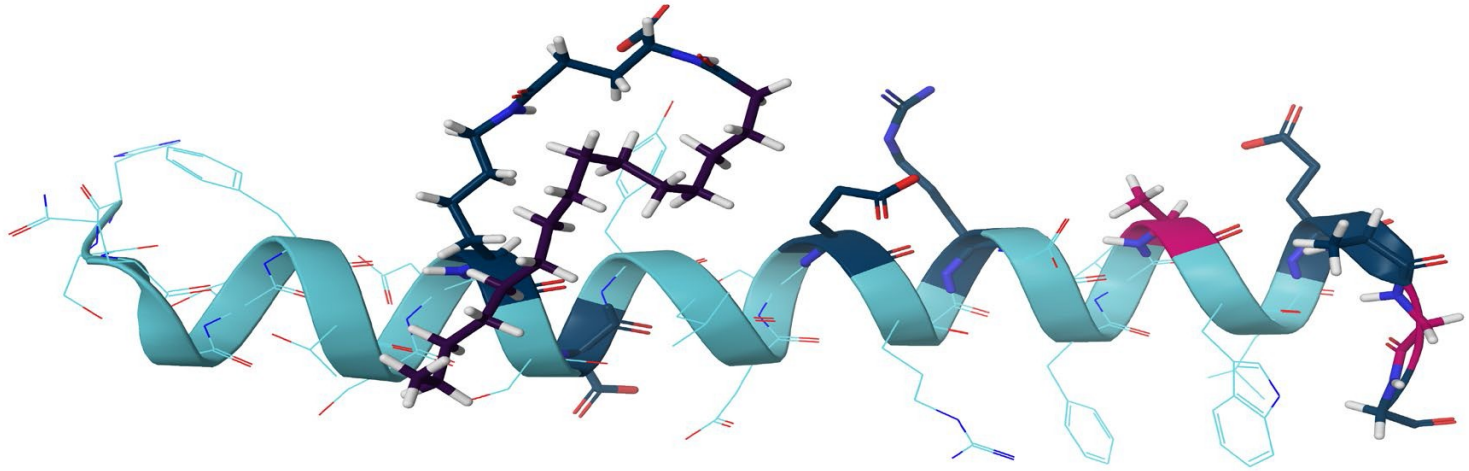
Data presented are "on-treatment without rescue medication" (efficacy estimand).
*p<0.05 vs dulaglutide 1.5 mg.
MMRM analysis. Abbreviations: A1C = glycated hemoglobin; B = baseline; Dula = dulaglutide; ETD, estimated treatment difference vs. 1.5 mg at 36 weeks; LS = least-squares.

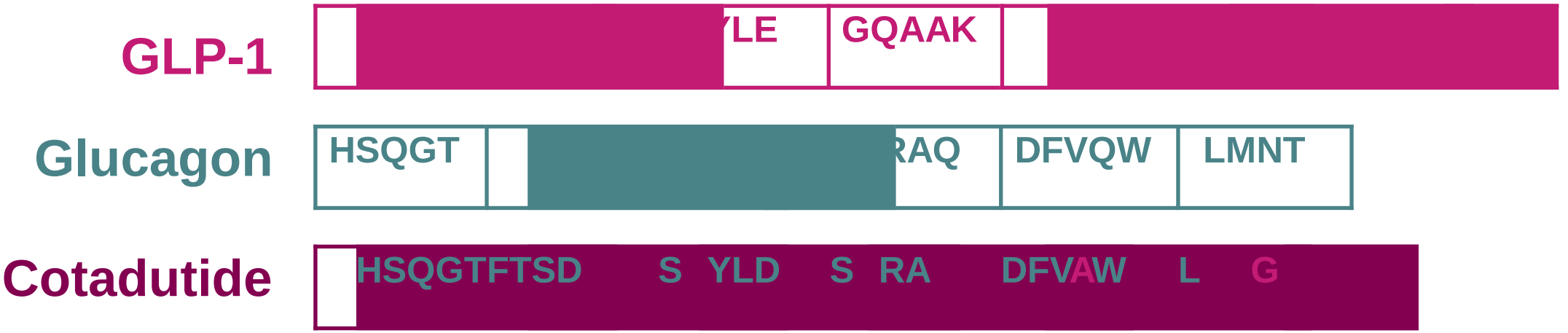
Frias J et al. 357-OR 80th Scientific Sessions. June 12-16, 2020. Chicago

DUAL AGONISTS

Two is meglio che One

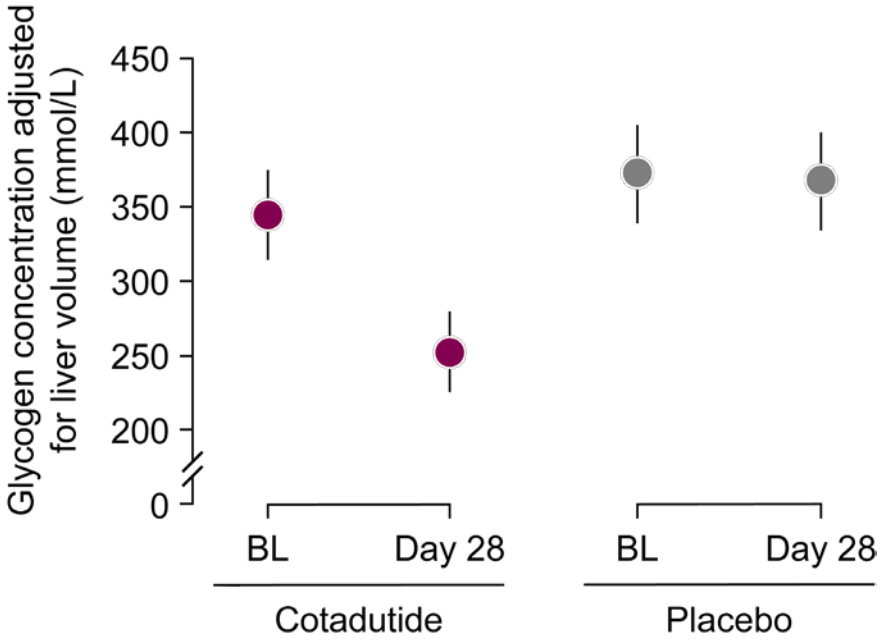
Cotadutide: A dual receptor agonist with GLP-1 and glucagon activity

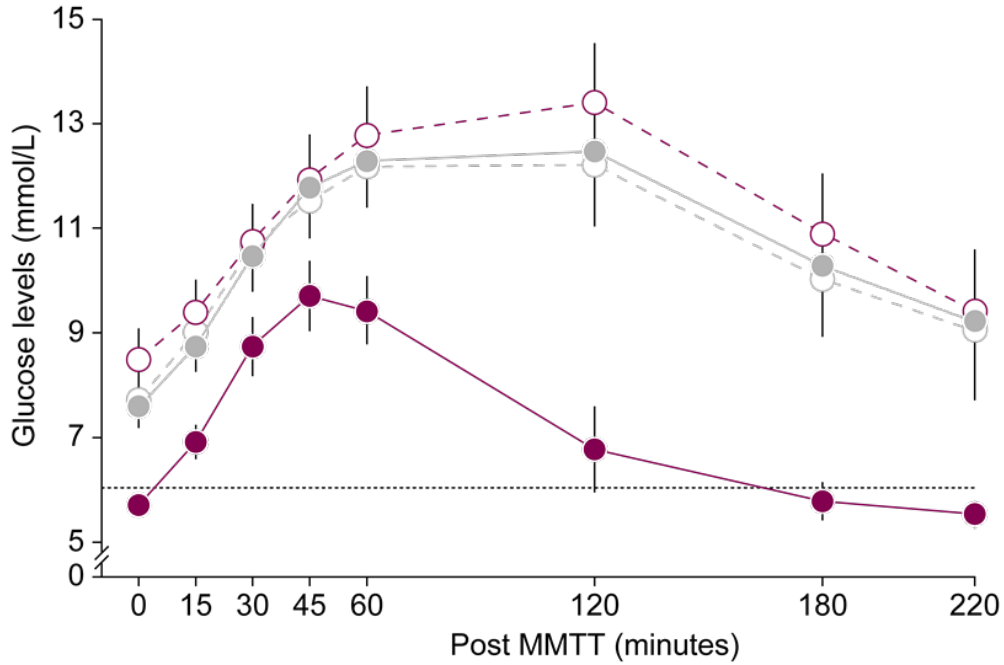




Ambery P et al. *Lancet.* 2018;391:2607–2618.
Amino acid sequence from Henderson et al. *Diabetes Obes Metab.* 2016;18:1176–1190.
GLP-1, glucagon-like peptide-1.

Cotadutide promoted a significant reduction in postprandial hepatic glycogen after a standardised meal

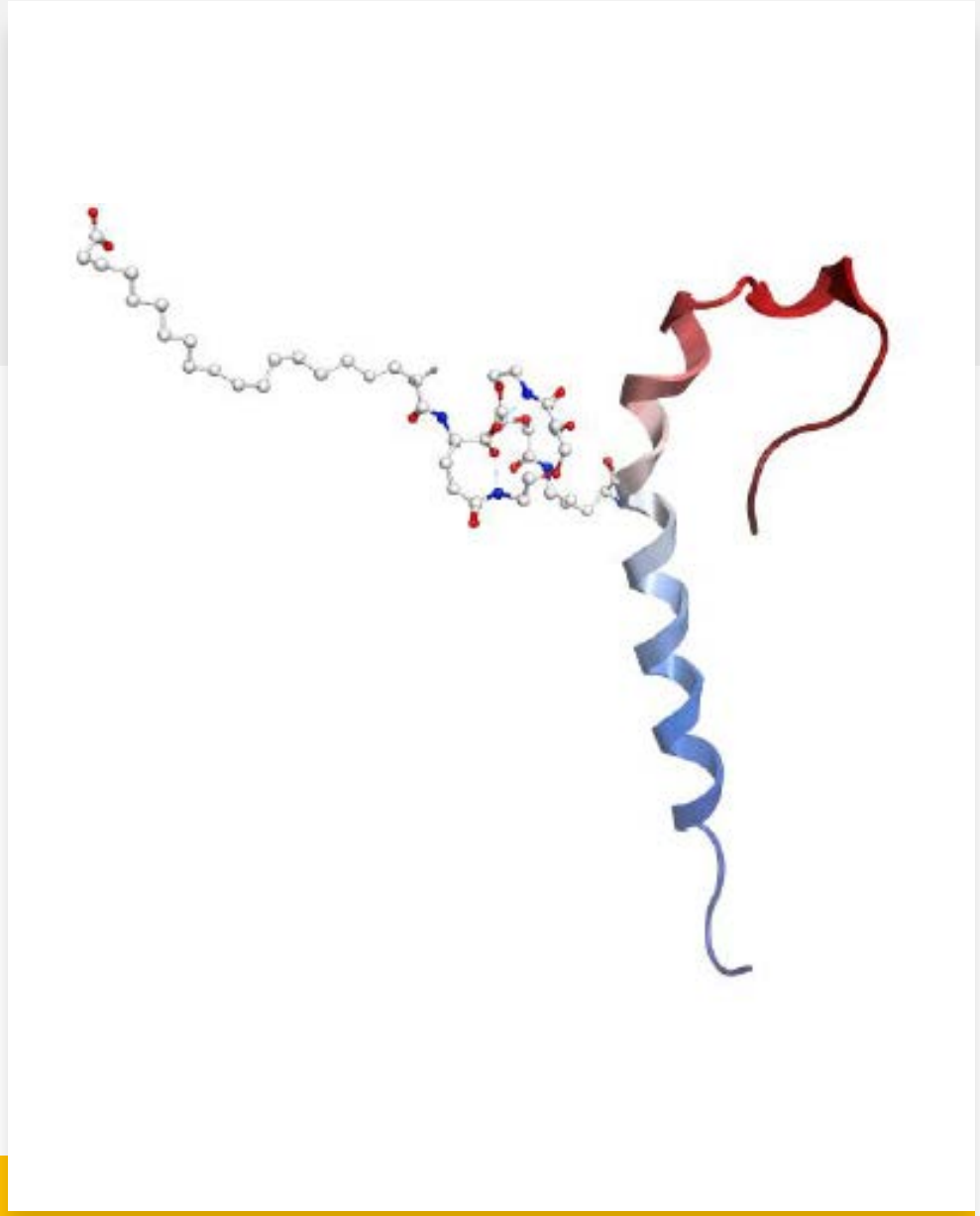




Cotadutide promoted significant reductions in fasting and postprandial glucose levels

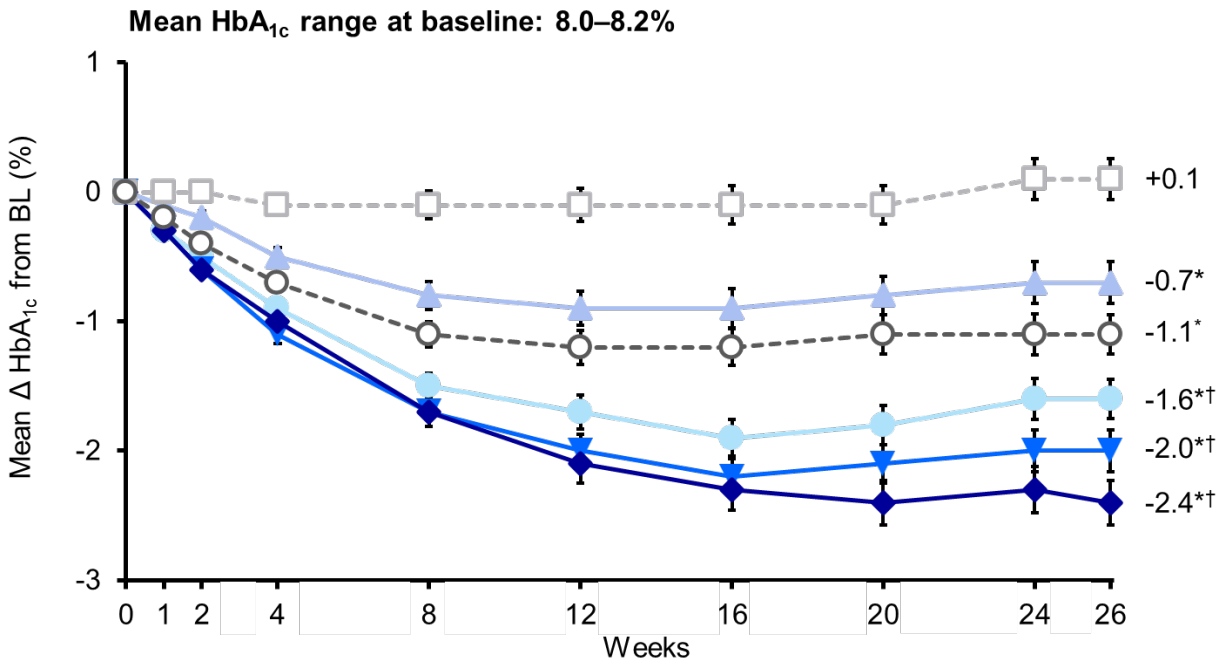
Tirzepatide: Dual GIP/GLP-1 receptor agonist

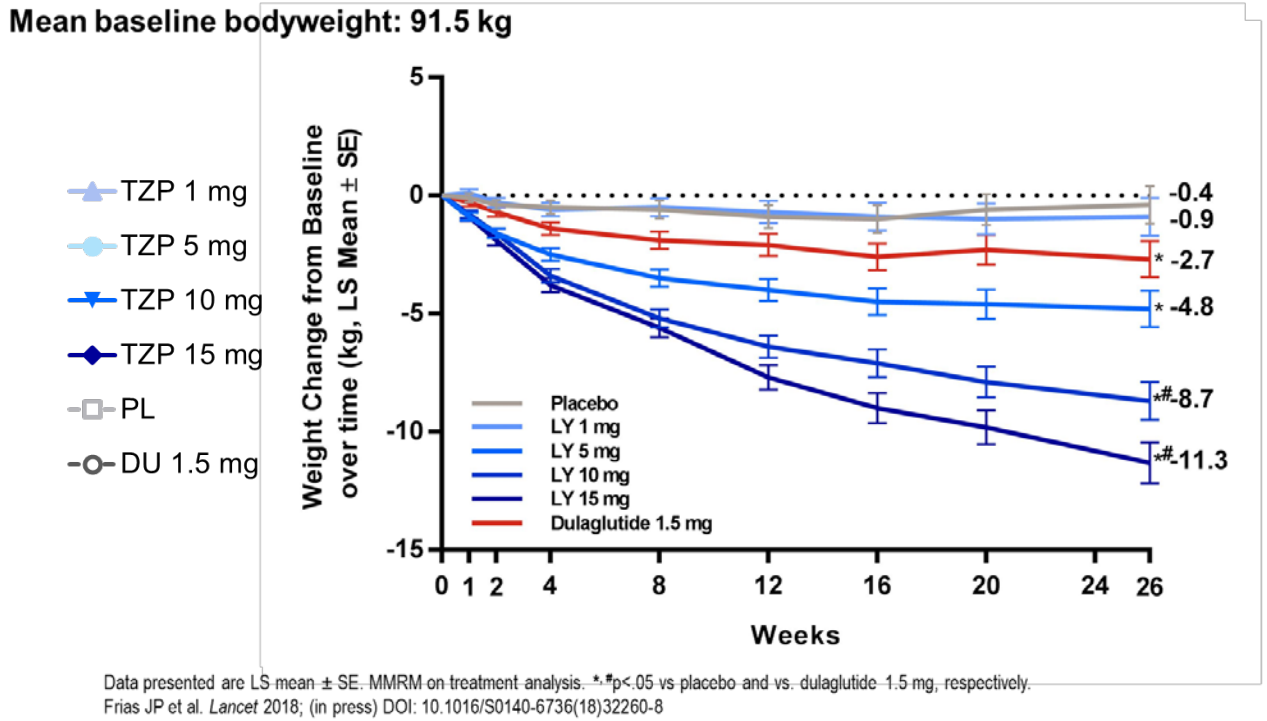
- Tirzepatide is a multi-functional peptide based on the native GIP peptide sequence, modified to bind to both GIP and GLP-1 receptors
- Tirzepatide is a 39 amino acid linear peptide and includes a C20 fatty diacid moiety
- *In vitro*, it has higher potency to native GIP and is less potent to native GLP-1
- Tirzepatide has a mean half-life of ~5 days (116.7 h), enabling once-weekly dosing



Coskun T, et al. *Mol Metab* 2018;18:3-14

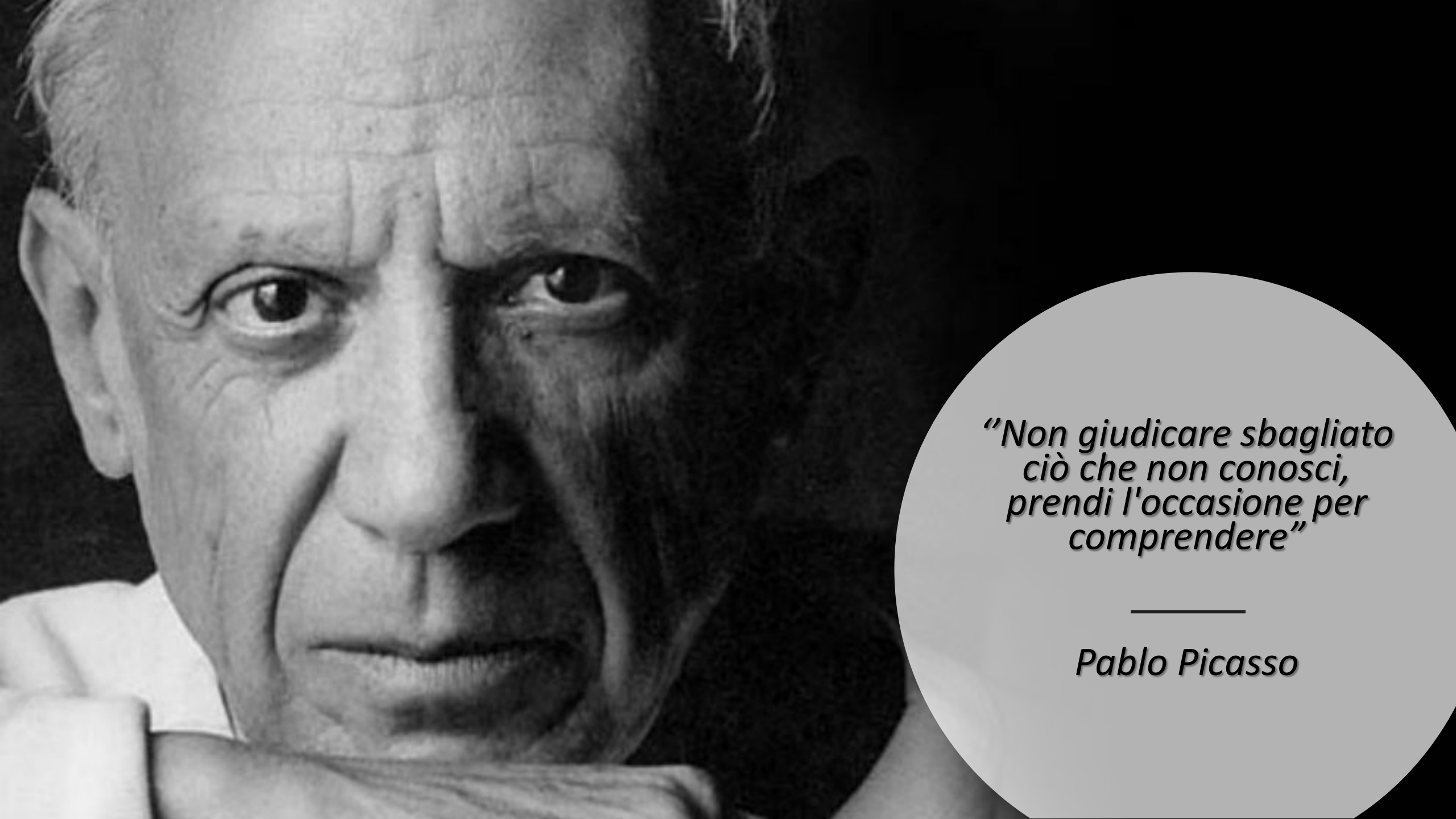
TIRZEPATIDE (GLP-1+GIP) HbA1c & Body Weight reduction





Data presented are LS mean ± SE. MMRM on treatment analysis. *,#p<.05 vs placebo and vs. dulaglutide 1.5 mg, respectively.
Frias JP et al. *Lancet* 2018; (in press) DOI: 10.1016/S0140-6736(18)32260-8

MMRM analysis, mITT on-treatment population
Values reported are LSM (SE). *p<0.05 vs PL; †p<0.05 vs DU 1.5 mg
Frias JP, et al. *Lancet* 2018;392(10160):2180-2193



“Non giudicare sbagliato ciò che non conosci, prendi l'occasione per comprendere”

Pablo Picasso