SID Società Italiana di Diabetologia
fondata nel 1964

Terapia con analoghi del GLP-1: quando e perché
II FASE - Bologna, 19 novembre 2019

POSSIAMO PUNTARE ANCORA DI PIÙ SUL CALO PONDERALE?

PAOLO SBRACCIA

Dipartimento di Medicina dei Sistemi
UOC di Medicina Interna
Centro per la Cura dell'Obesità
Policlinico Tor Vergata

Rete Centri Accreditati per la Cura dell'Obesità — SIO Società Italiana dell'Obesità

TOR VERGATA UNIVERSITÀ DEGLI STUDI DI ROMA

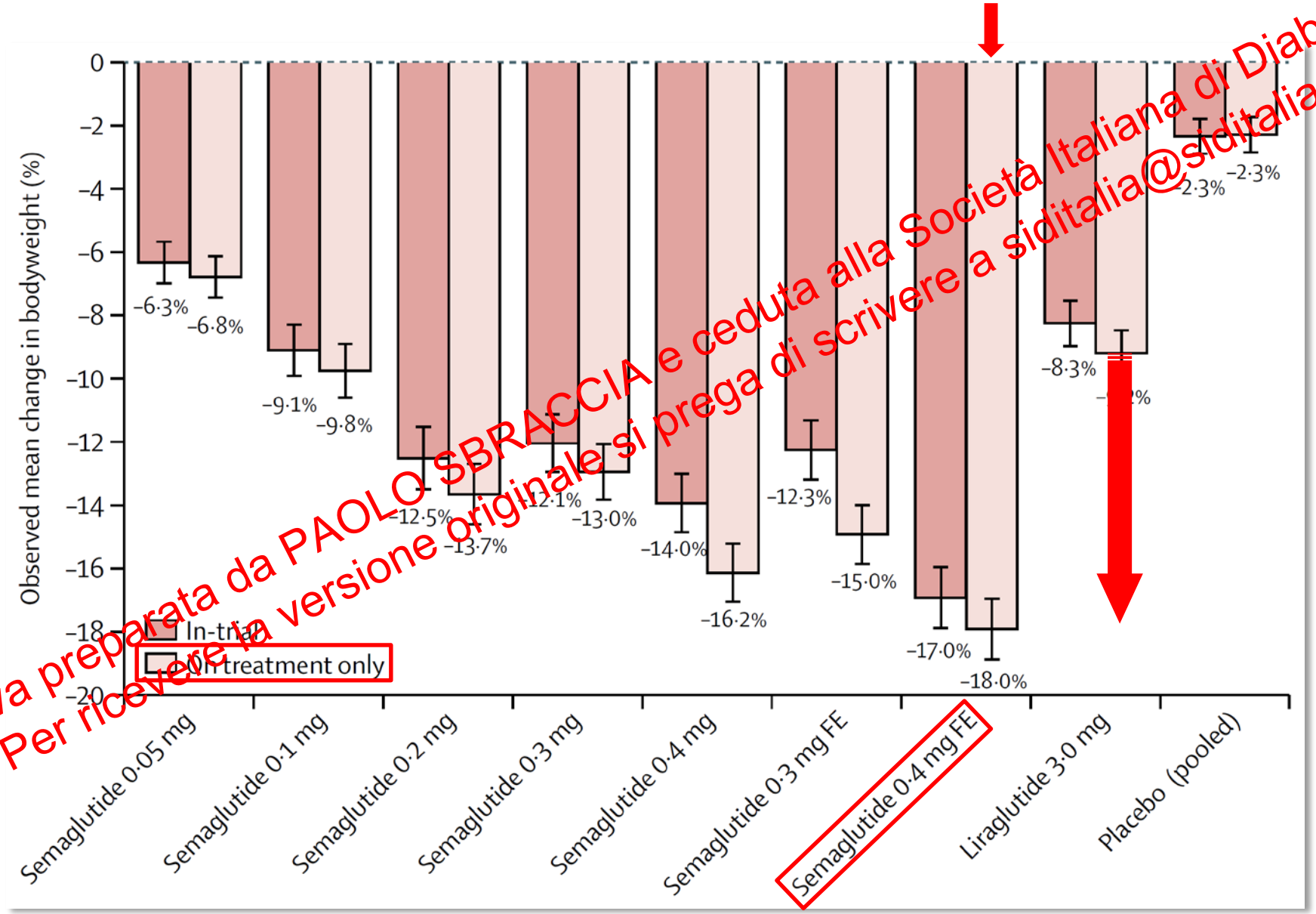
PTV Fondazione Policlinico Tor Vergata

EASOCOM EASO Collaborating Centre for Obesity Management

Dichiara di aver ricevuto negli ultimi due anni compensi dalle seguenti Aziende Farmaceutiche:

- Novo Nordisk
- Bruno Farmaceutici
- Orexigen
- Astra Zeneca

EFFICACY AND SAFETY OF SEMAGLUTIDE COMPARED WITH LIRAGLUTIDE FOR WEIGHT LOSS IN PATIENTS WITH OBESITY



Data at week 52

O'Neil et al, Lancet, 2018

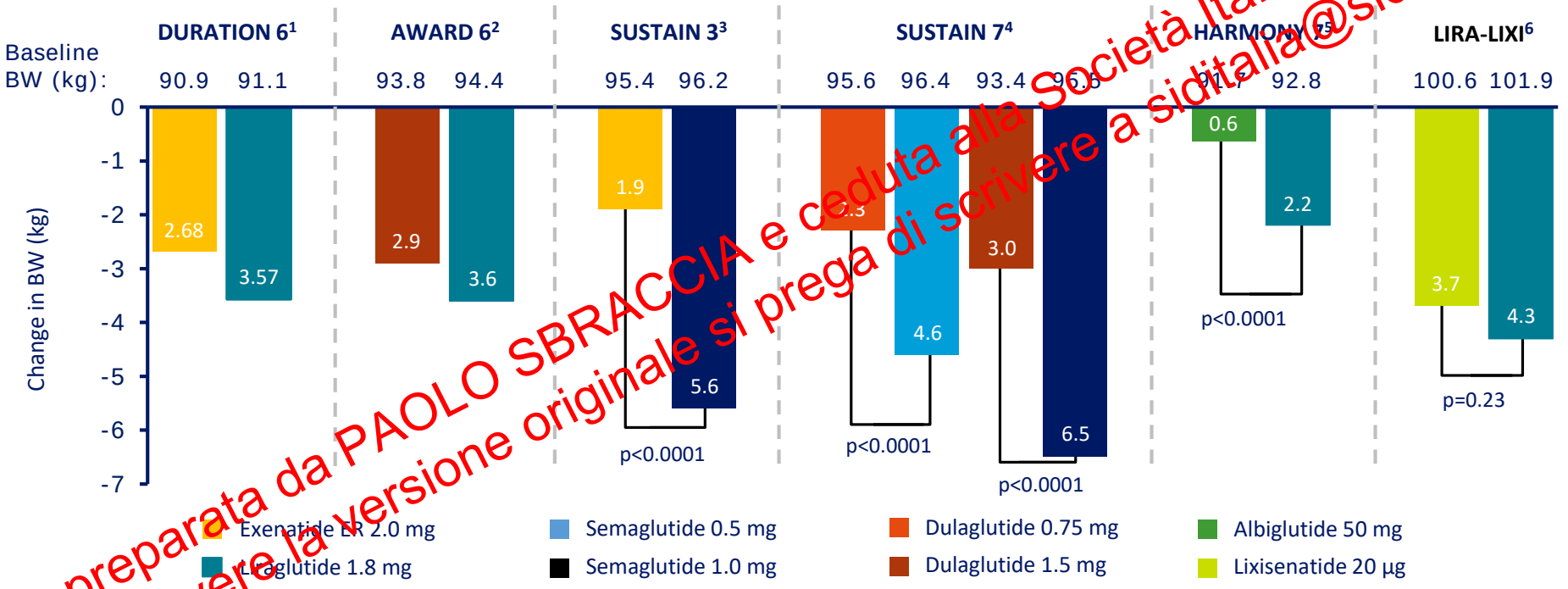
POSSIAMO PUNTARE ANCORA DI PIU SUL CALO PONDERALE?

POSSIAMO PUNTARE ANCORA DI PIU SUL CALO PONDERALE?

Is Success in Diabetes Possible Without Obesity Care?

GLP-1RAs reduce Body Weight

- RESULTS FROM COMPARATIVE TRIALS



- 1. Buse JB et al. *Lancet* 2013;381:117–24; 2. Dungan KM et al. *Lancet* 2014;384:1349–57; 3. Ahmann AJ et al. *Diabetes Care* 2018;41:258–66; 4. Pratley RE et al. *Lancet Diabetes Endocrinol* 2018;6:275–86; 5. Pratley RE et al. *Lancet Diabetes Endocrinol* 2014;2:289–97; 6. Nauck M et al. *Diabetes Care* 2016;39:1501–9.

SUSTAIN FORTE will evaluate high-dose semaglutide in type 2 diabetes and is expected to conclude by end of 2020

SUSTAIN FORTE trial design

Randomised: 964 patients with type 2 diabetes

- **Semaglutide 2.0 mg**
- **Semaglutide 1.0 mg**

40 weeks

Trial objective

To establish the effect of semaglutide sc 2.0 mg QW vs. semaglutide 1.0 mg QW on glycaemic control in patients with type 2 diabetes on a background of metformin with or without SU treatment

High-dose semaglutide

- Supports individualised treatment
- Offers a simple treatment regimen for intensification

Key SUSTAIN FORTE trial inclusion criteria

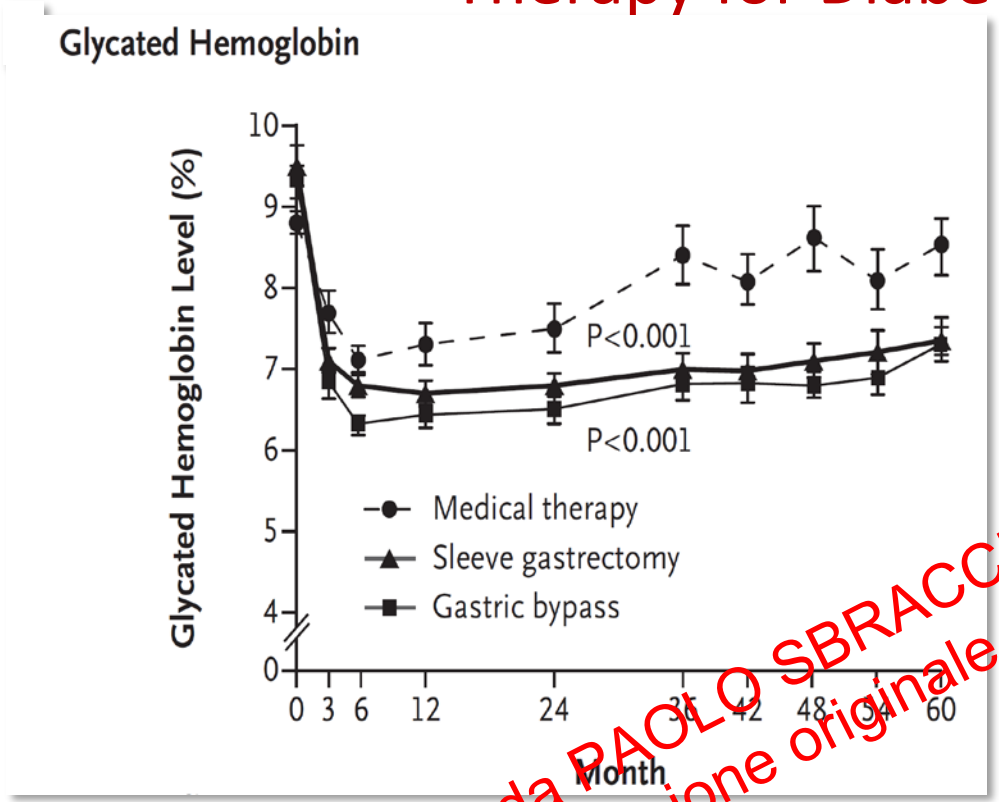
People with type 2 diabetes from **10 countries**

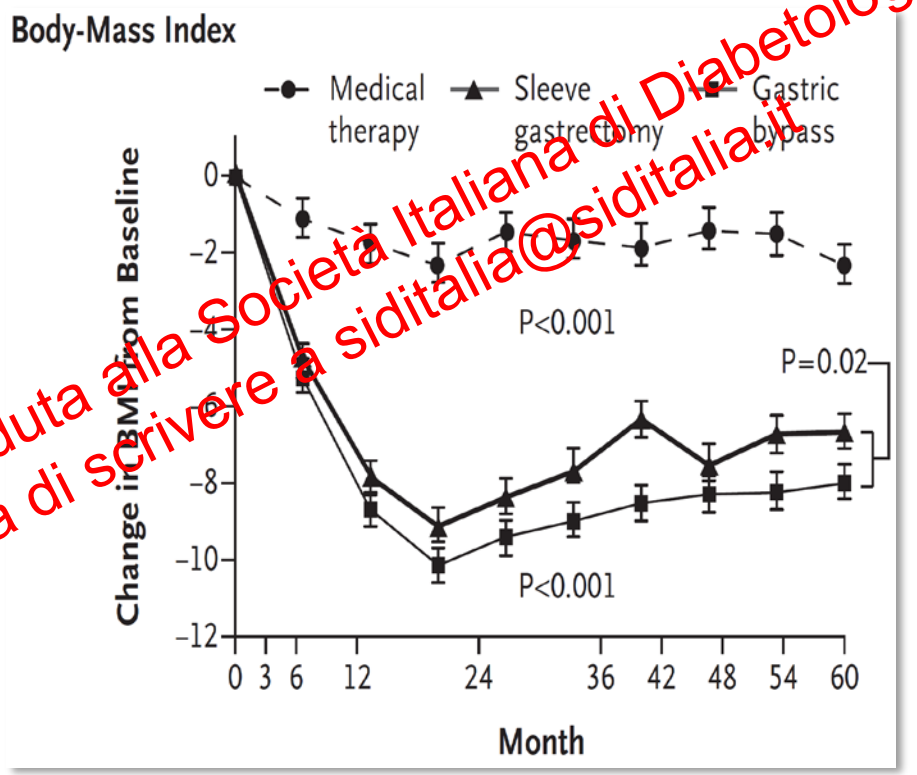
- HbA_{1c} 8-10%
- Stable dose of metformin +/- SU

Trial initiation: Q2 2019

sc: subcutaneous; QW: once-weekly; SU: sulphonylurea

Bariatric Surgery versus Intensive Medical Therapy for Diabetes — 5-Year Outcomes



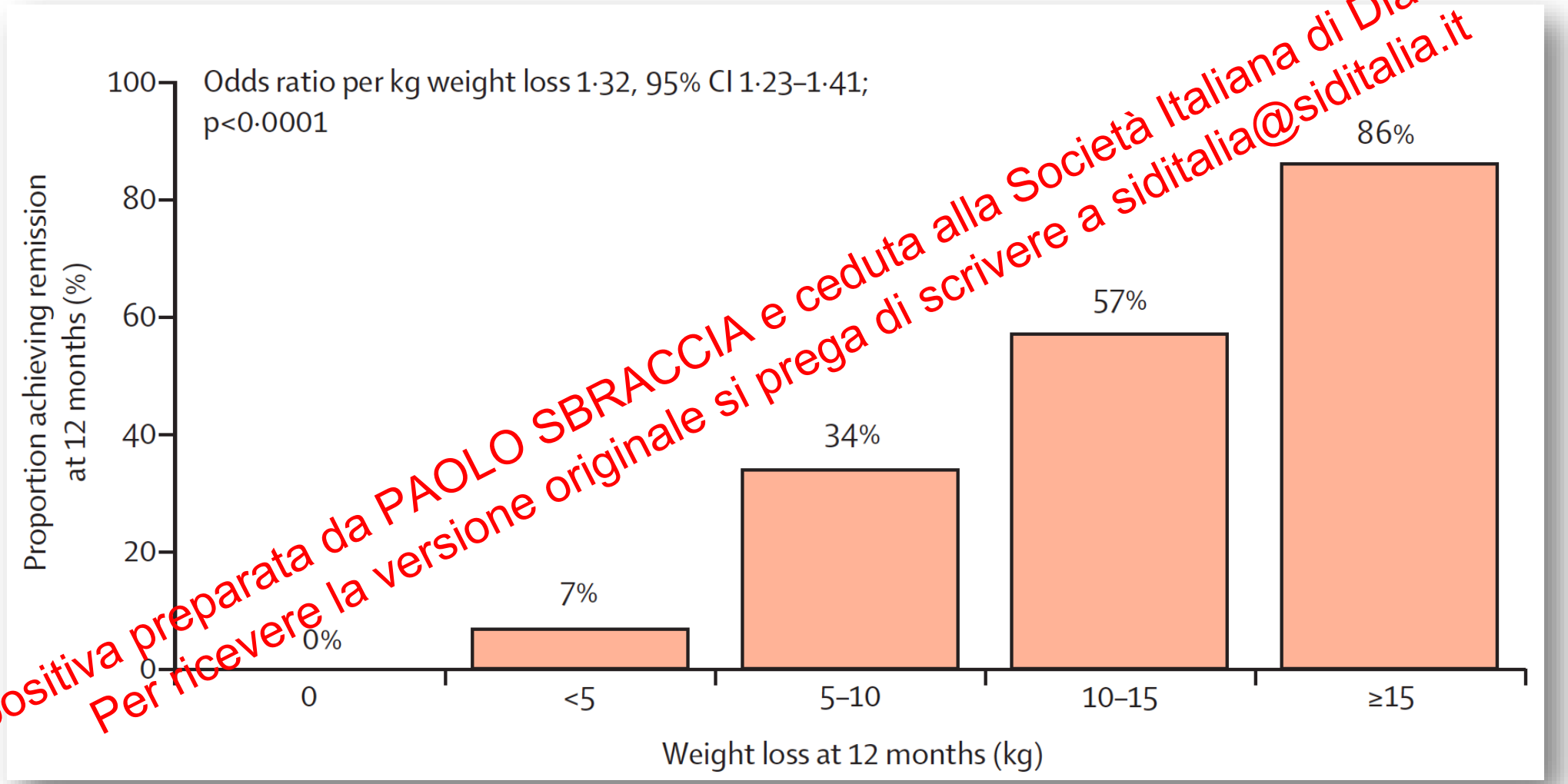


Weight loss by year 1 correlated with success in achieving the primary end point.

Surgical **T**reatment and **M**edications **P**otentially **E**radicate **D**iabetes **E**fficiently (***STAMPEDE***)

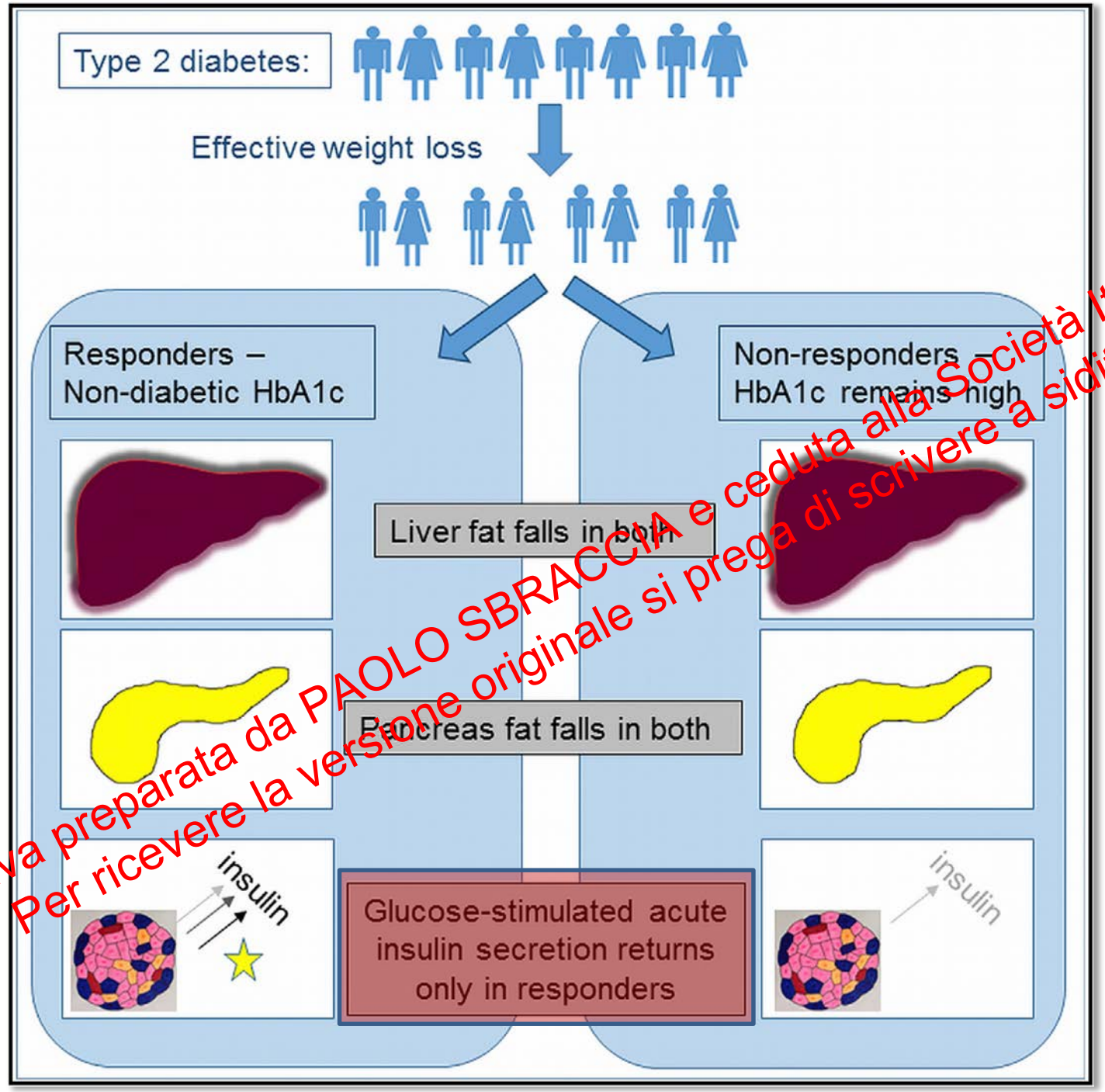
Schauer et al, New Engl J Med 2017

Primary Care-led Weight Management for Remission of Type 2 Diabetes (DiRECT)



Lean MEJ et al, Lancet 2017

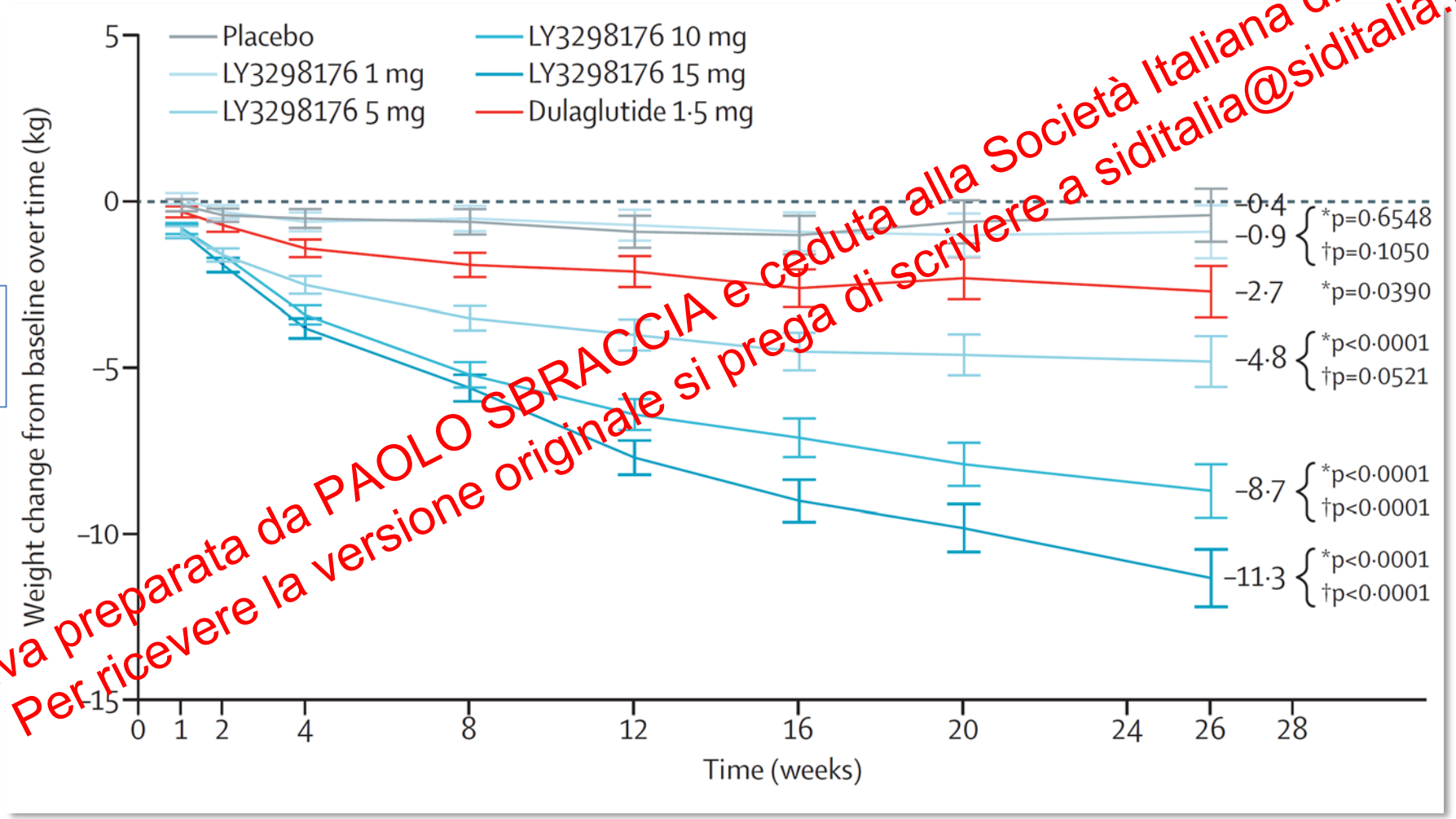
DiRECT



Taylor R et al,
Cell Metab 2018

Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial

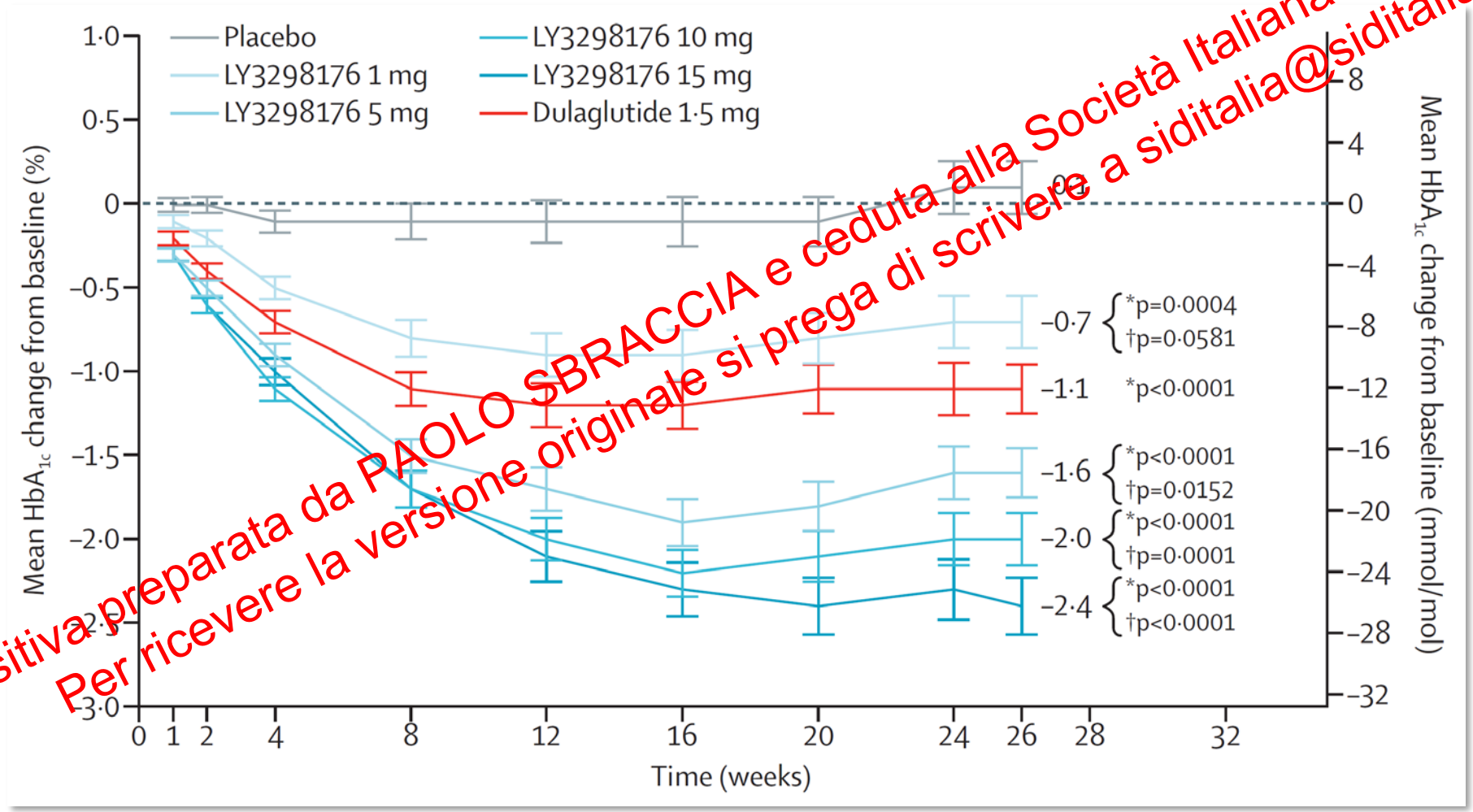
Weight change (Kg)



Frias et al, Lancet, 2018

Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial

HbA1c (%)



Frias et al, Lancet, 2018

PIPELINES

New anti-obesity drugs under investigation

Centrally acting agents

Setmelanotide
Velneperit (Discontinued)
Zonisamide-bupropion
Cannabinoid type-1 receptor blockers

Gut hormones and incretin effects

Semaglutide
Amylin mimetics
GIP analogue
Dual action GLP-1/Glucagon RA
Triple combination glucagon-GIP-GLP-1 agonist
PYY
Leptin analogues

Other novel targets

Beloranib (Discontinued)
Lipase inhibitor: Cetilistat
Triple monoamine reuptake inhibitor: Tesofensine
FGF

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Other novel targets

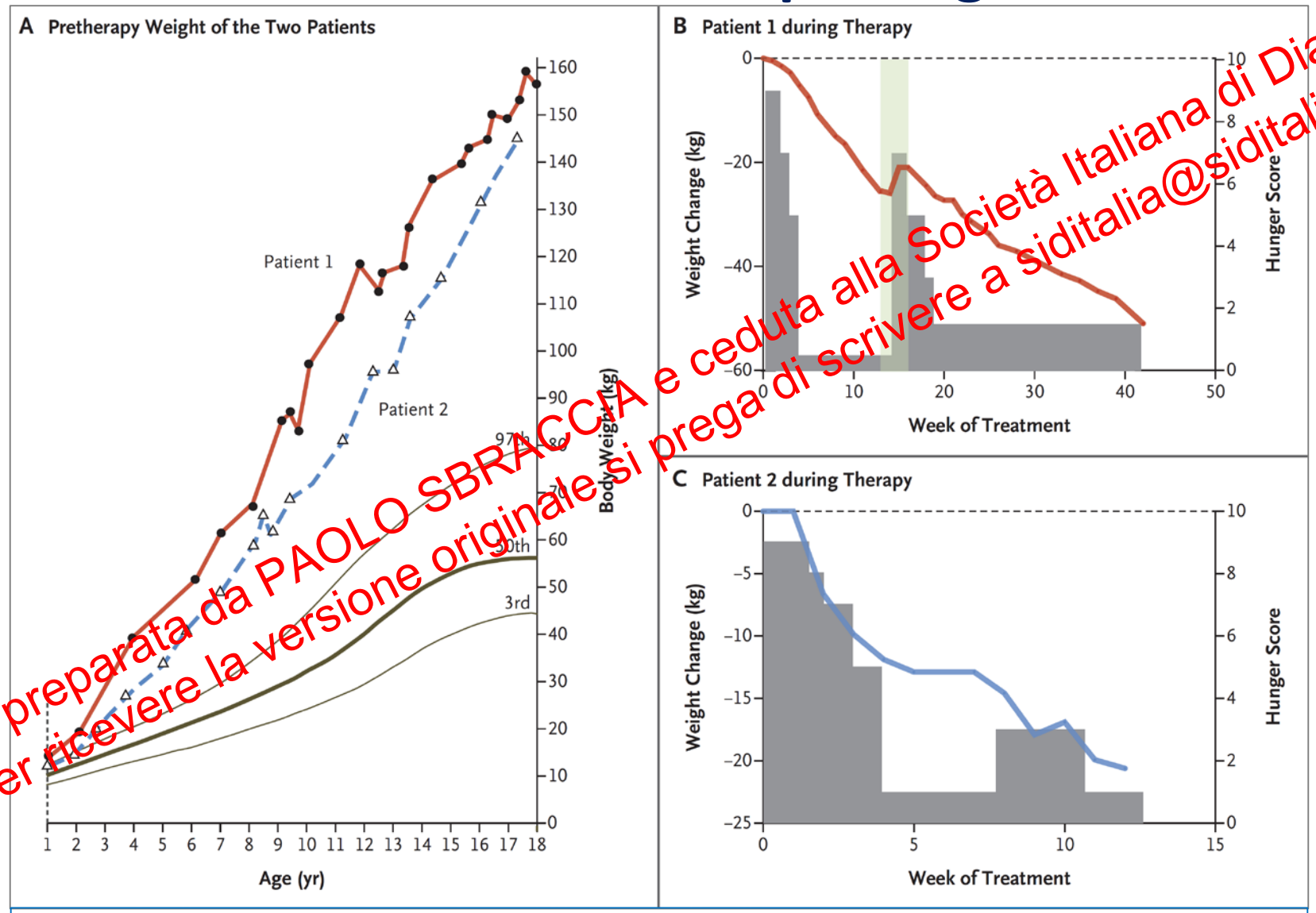
Beloranib (Discontinued)

Lipase inhibitor: Cetilistat

Triple monoamine reuptake inhibitor: Tesofensine

FGF

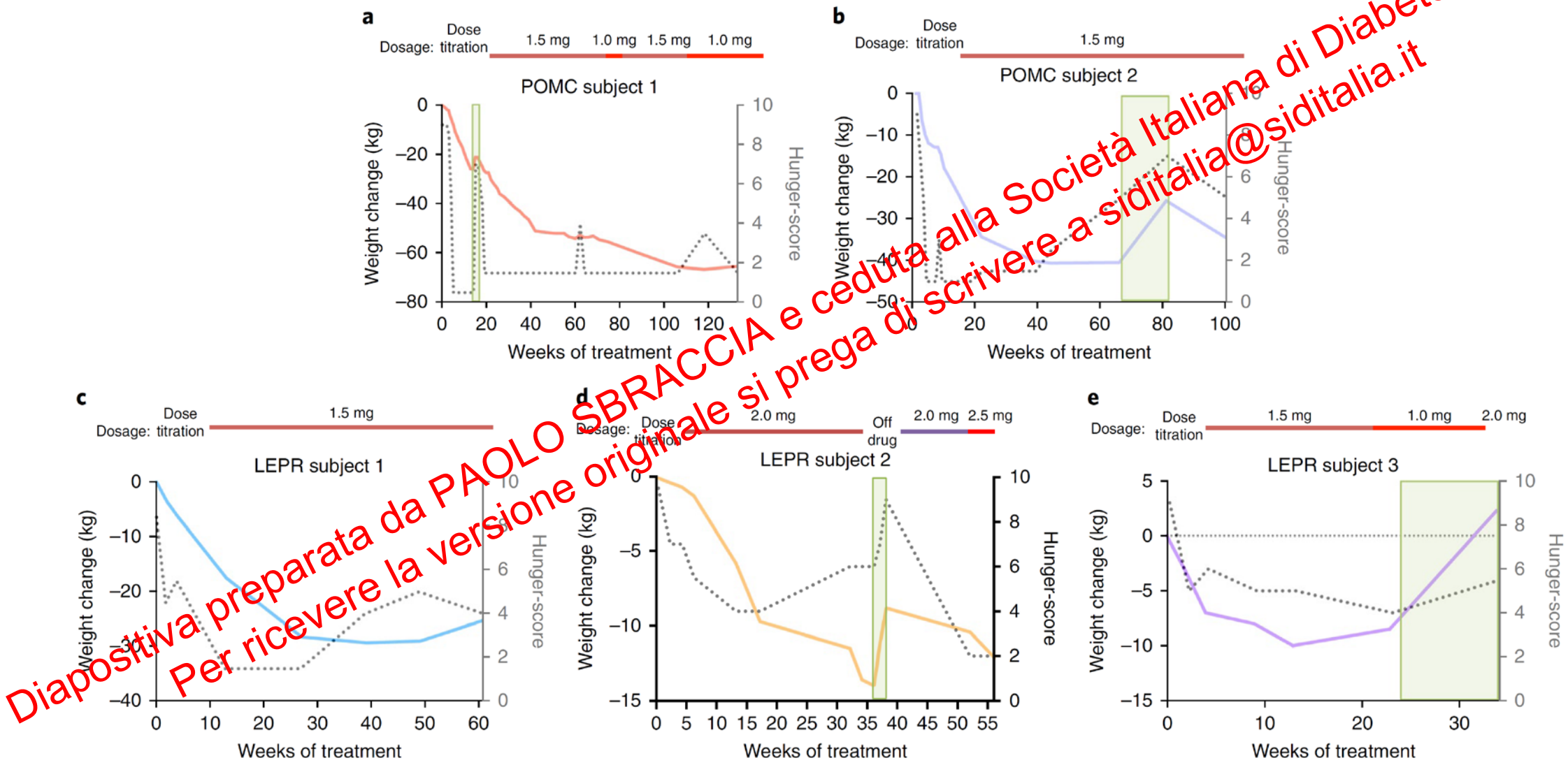
Proopiomelanocortin Deficiency Treated with a Melanocortin-4 Receptor Agonist



Pretherapy Weight and Changes in Weight and Hunger Scores during Therapy

Kühnen P et al, N Engl J Med, 2016

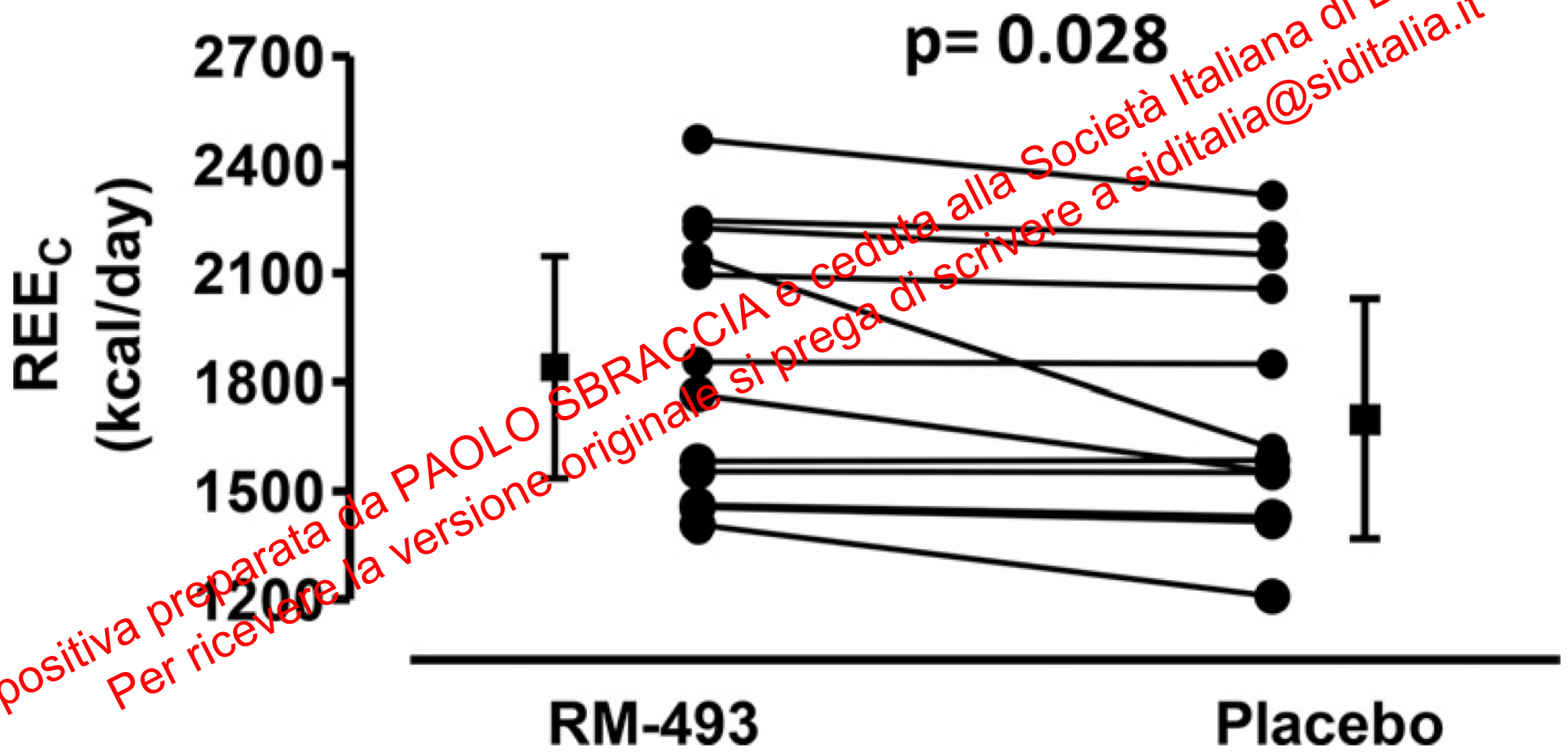
MC4R agonism promotes durable weight loss in patients with leptin receptor deficiency



Body weight course and hunger-score during setmelanotide treatment

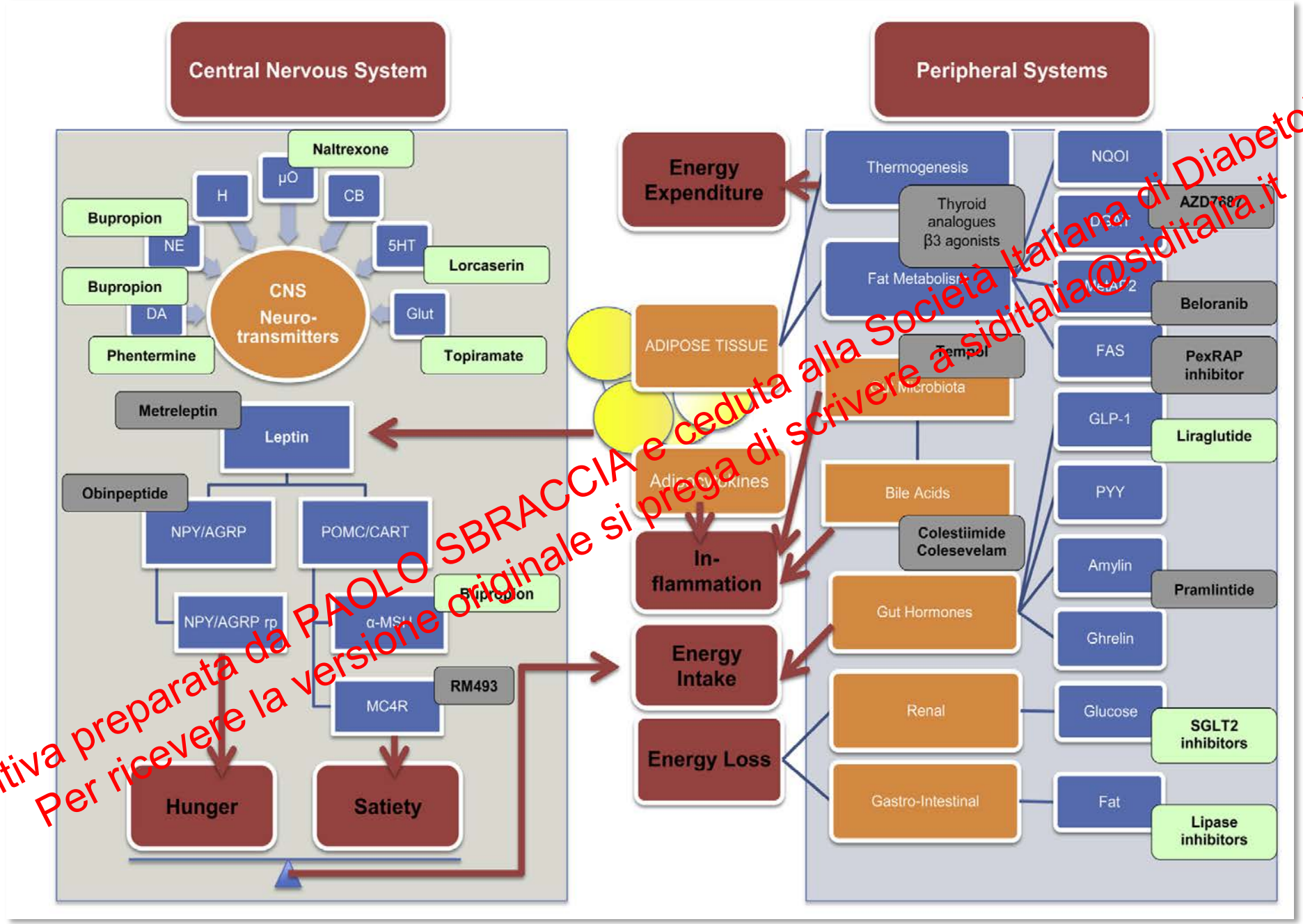
Clement K et al, Nature Med, 2018

RM-493, a Melanocortin-4 Receptor (MC4R) Agonist Increases Resting Energy Expenditure in Obese Individuals



Effect of RM-493 vs placebo on REE at the end of the treatment period

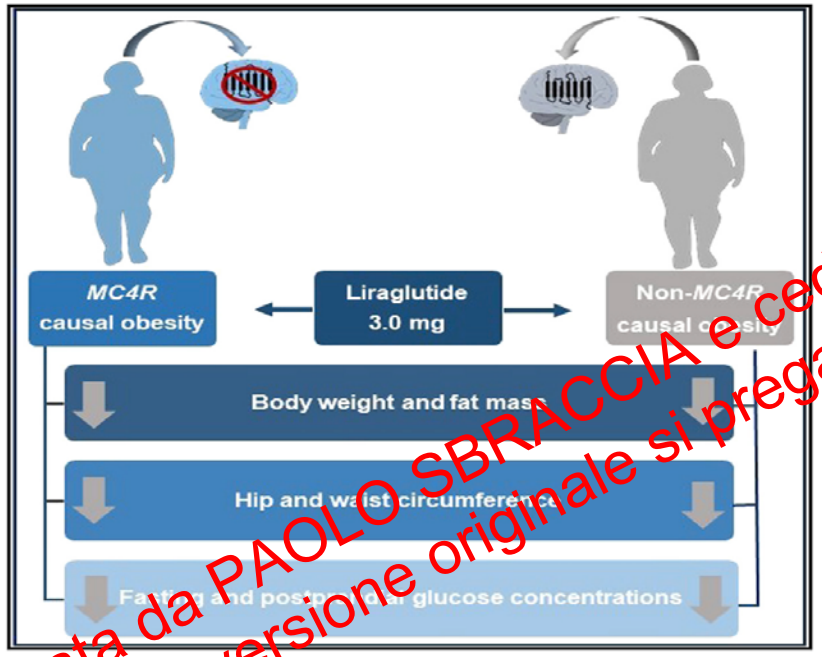
Kong Y et al, JCEM, 2015



Cell Metabolism

Patients with Obesity Caused by Melanocortin-4 Receptor Mutations Can Be Treated with a Glucagon-like Peptide-1 Receptor Agonist

Graphical Abstract



Highlights

- Fully functional MC4Rs are not required for GLP-1 RA-mediated weight loss
- Liraglutide caused a 6% weight loss in patients with *MC4R* mutations and controls
- Fat mass, waist circumference, and glucose concentrations improved with treatment
- Liraglutide is an effective treatment of the most common form of monogenic obesity

Authors

Eva W. Iepsen, Jinyi Zhang, Henrik S. Thomsen, ..., Jens J. Holst, Jens-Christian Holm, Signe S. Torekov

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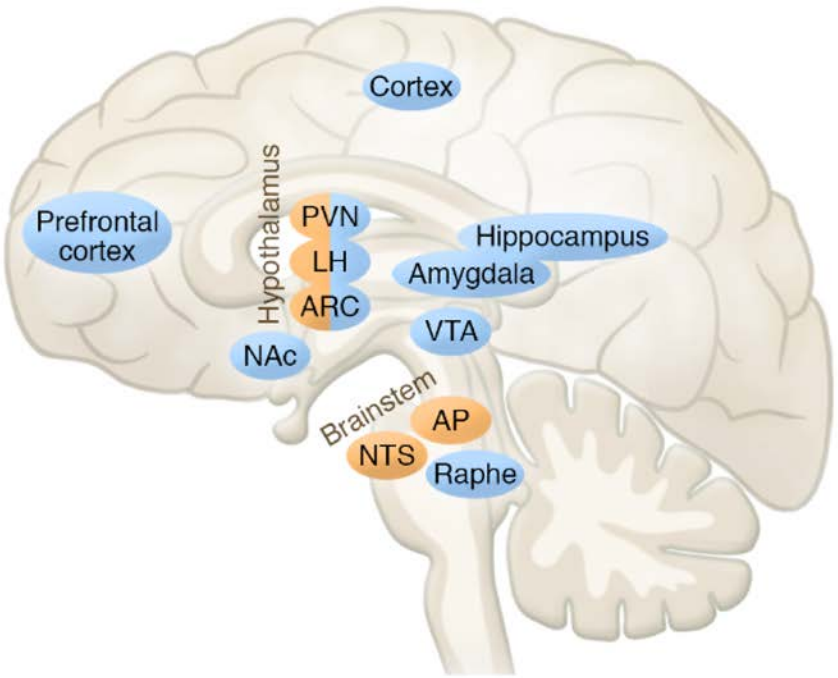
torekov@sund.ku.dk (S.S.T.)

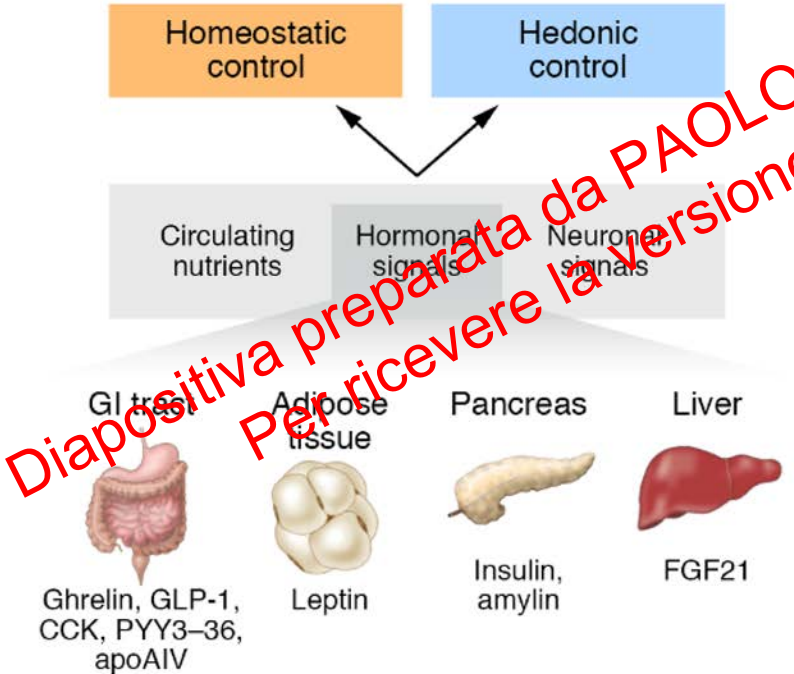
In Brief

Iepsen et al. show that the diabetes and obesity drug liraglutide, which has appetite-suppressing effects, caused weight loss in obese patients with mutations in the appetite-regulating *melanocortin-4 receptor* (*MC4R*). These results show that the appetite effects of liraglutide are independent of the MC4R pathway and offer therapeutic opportunities for patients with *MC4R* causal obesity.

JCI The Journal of Clinical Investigation

CNS-targeting pharmacological interventions for the metabolic syndrome





Stemmer K ... Tschop M, Obesity 2019

Published online: February 4, 2015

Research Article

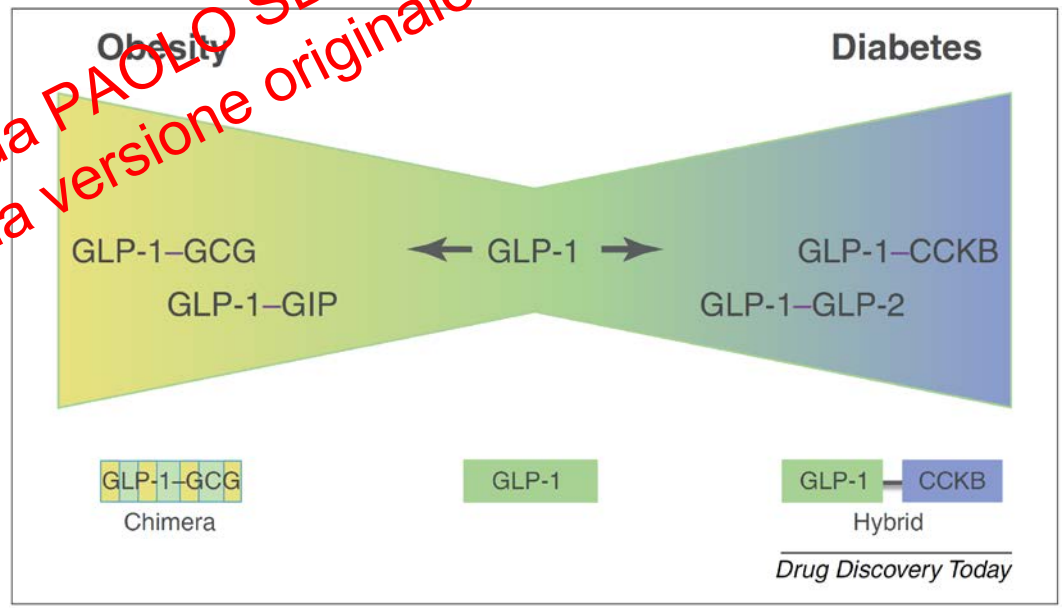
TRANSPARENT PROCESS OPEN ACCESS

EMBO Molecular Medicine

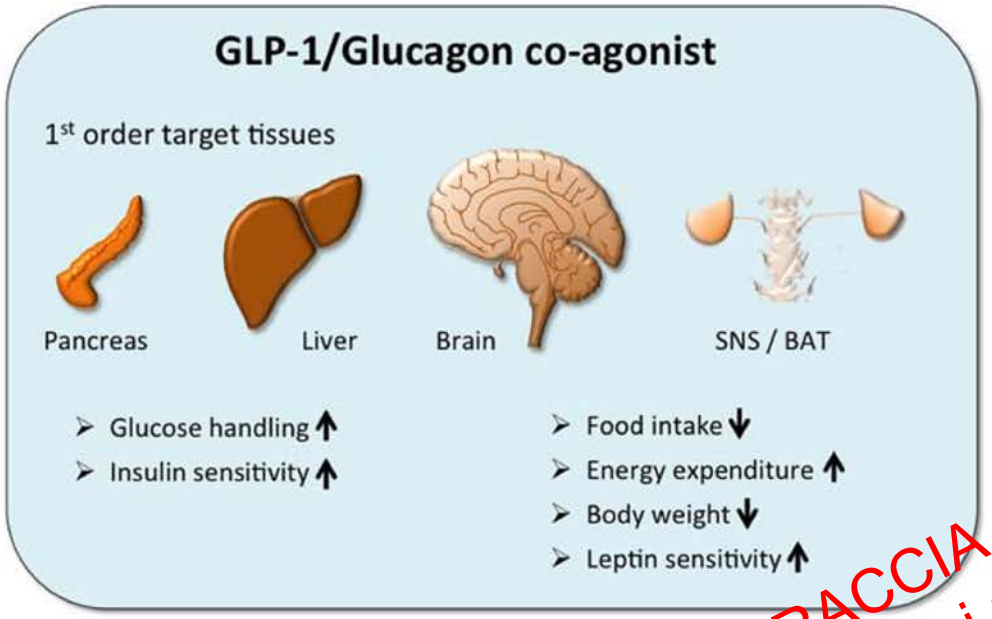
Dual melanocortin-4 receptor and GLP-1 receptor agonism amplifies metabolic benefits in diet-induced obese mice

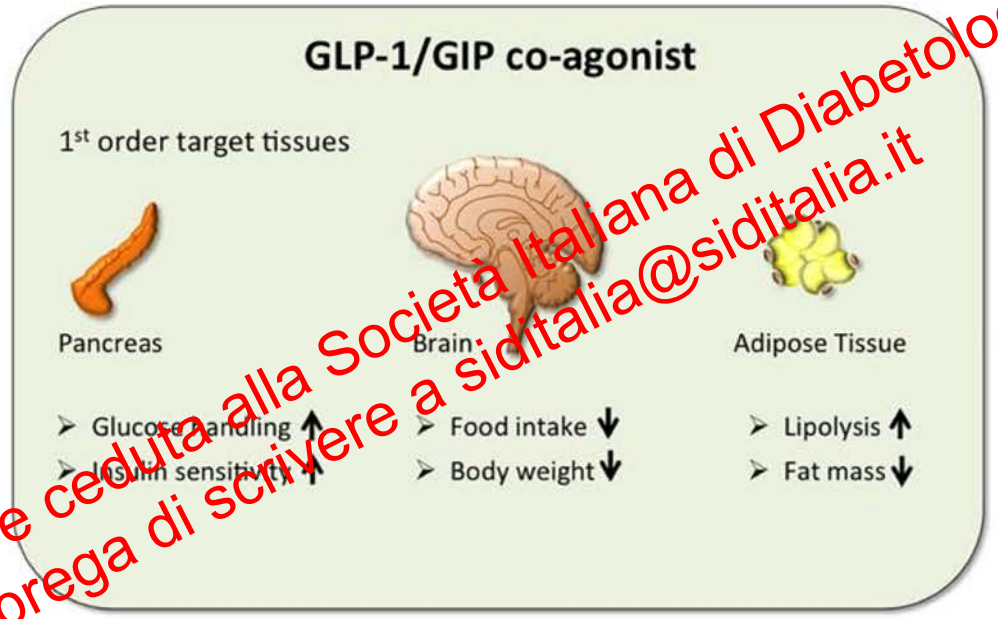
Christoffer Clemmensen[1,2], Brian Finan[1,2], Katrin Fischer[1,2], Robby Zachariah Tom[1,2], Beata Legutko[1,2], Laura Sehrer[1,2], Daniela Heine[1,2], Niklas Grassl[1,2], Carola W Meyer[1,2], Bart Henderson[4], Susanna M Hofmann[3], Matthias H Tschöp[1,2], Lex HT Van der Ploeg[4] & Timo D Müller[1,2,*]

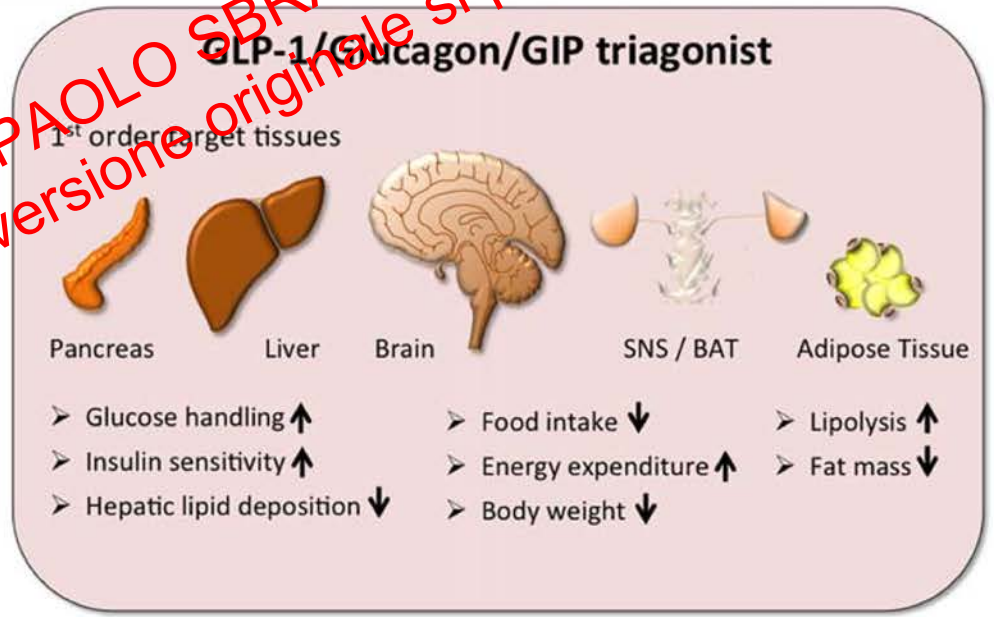
MULTIFUNCTIONAL PEPTIDES



EMERGING POLY-AGONISTS FOR OBESITY AND TYPE 2 DIABETES







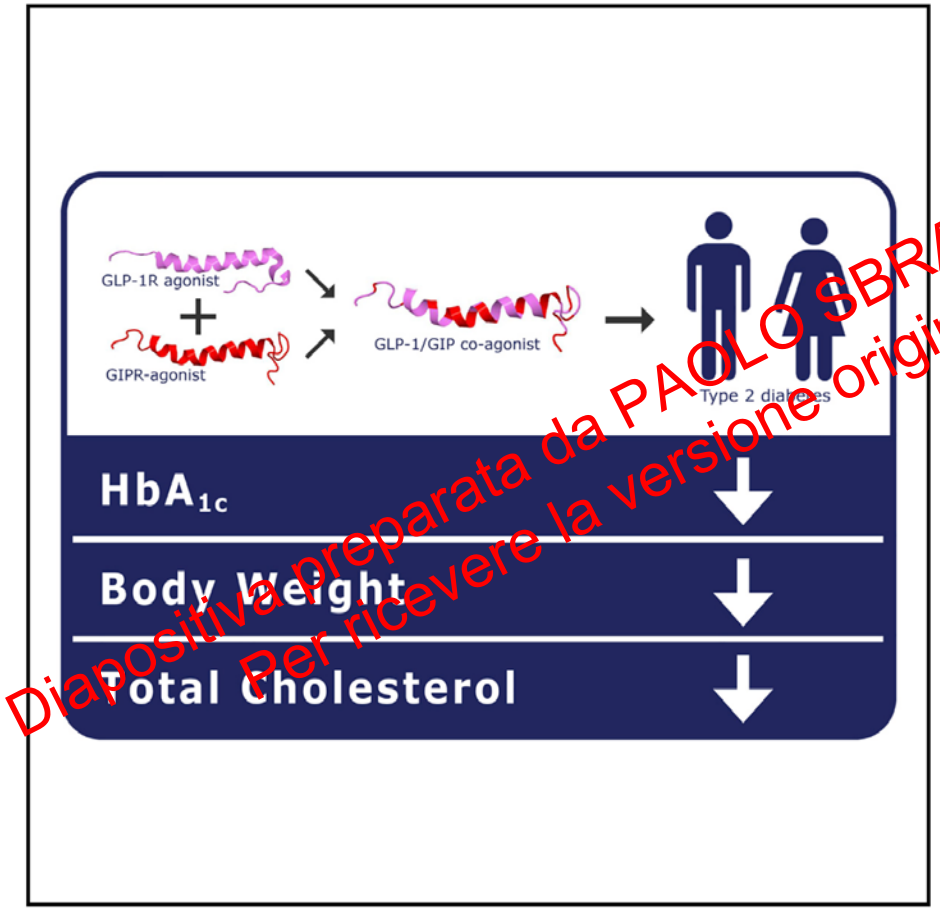
Kleinert M ... Tschop M, Obesity 2017

Clinical and Translational Report

Cell Metabolism

The Sustained Effects of a Dual GIP/GLP-1 Receptor Agonist, NNC0090-2746, in Patients with Type 2 Diabetes

Graphical Abstract



Authors

Juan Pablo Frias, Edward J. Bastyr III, Louis Vignati, ..., Klara Lawen, Rune Haubo Christensen, Richard D. DiMarchi

Correspondence

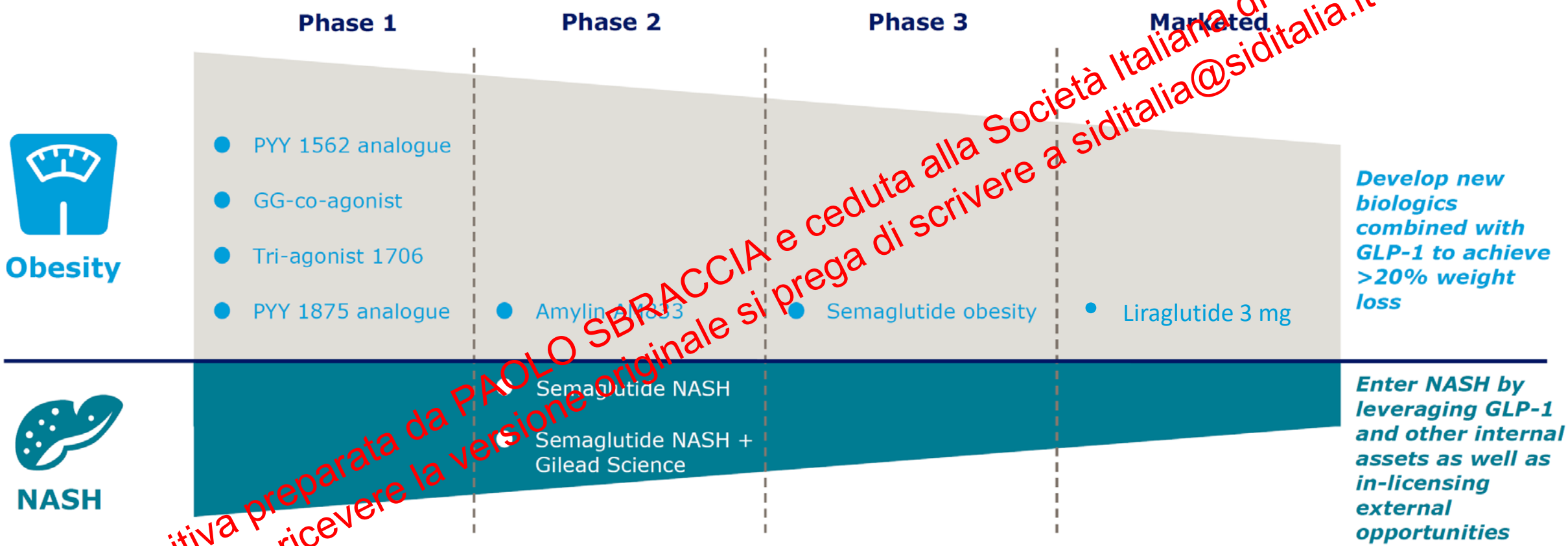
rdmh@novonordisk.com

In Brief

Frias et al. assessed the effects of NNC0090-2746, a unimolecular dual agonist derived from hybridized GLP-1 and GIP, in patients with T2DM. NNC0090-2746 was well tolerated and significantly improved glycemic control and reduced body weight compared with placebo. Maximum benefit was obtained by patients with the best baseline glycemic control.

Cell Metab 2017

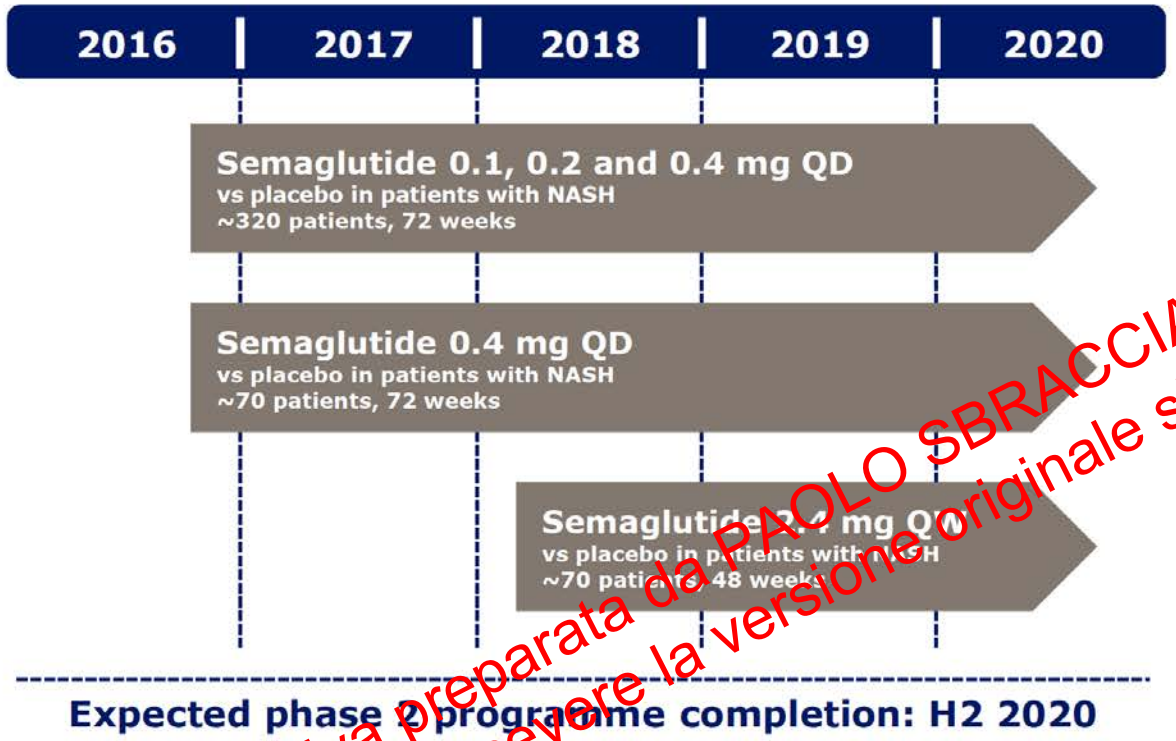
Clinical projects in obesity and NASH



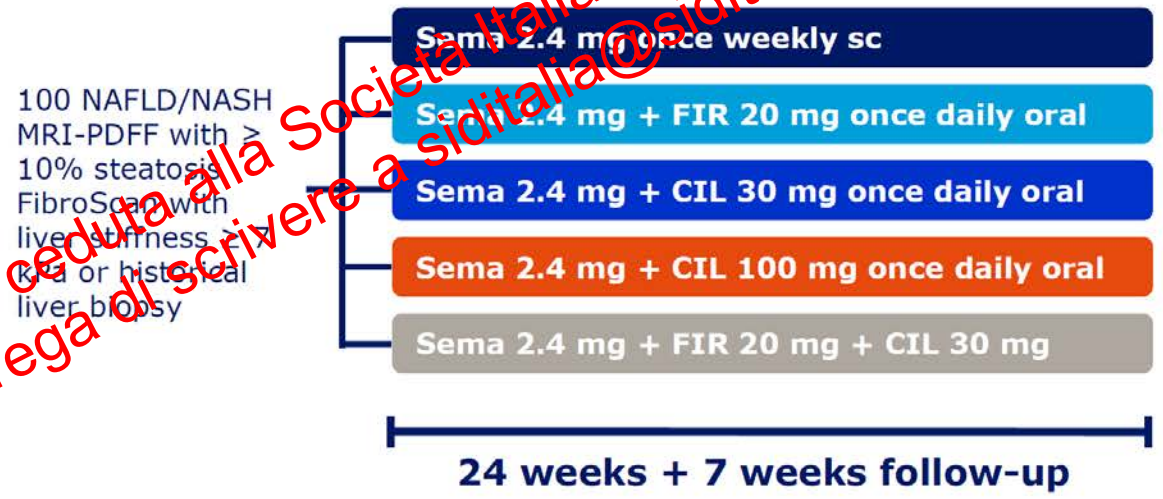
PYY: peptide YY; GG: GLP-1 and glucagon; NASH: nonalcoholic steatohepatitis; GLP-1: glucagon-like peptide-1

Novo Nordisk is investigating opportunities within NASH

Semaglutide NASH phase 2 programme



Proof of concept phase 2 combination trial design



Trial information

- Safety and tolerability trial
- Initiation Q3 2019
- MRI-PDFF, MRE & biomarkers at least at: 0, 12, 24 weeks

QD: Once daily; QW: once-weekly; sc: subcutaneous; MRI-PDFF: magnetic resonance imaging–estimated proton density fat fraction; MRE: magnetic resonance elastography; NASH: nonalcoholic steatohepatitis; NAFLD: Nonalcoholic fatty liver disease; kPa: kilopascals; FIR: firsocostat (ACC inhibitor); CIL: cilofexor (FXR agonist); ACC: acetyl-CoA carboxylase; FXR: Farnesoid X receptor

New anti-obesity drugs under investigation

Centrally acting agents

Setmelanotide
Velneperit (Discontinued)
Zonisamide-bupropion
Cannabinoid type-1 receptor blockers

Other novel targets

Beloranib (Discontinued)
Lipase inhibitor: Cetilistat
Triple monoamine reuptake inhibitor: Tesofensine
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Gut hormones and incretin effects

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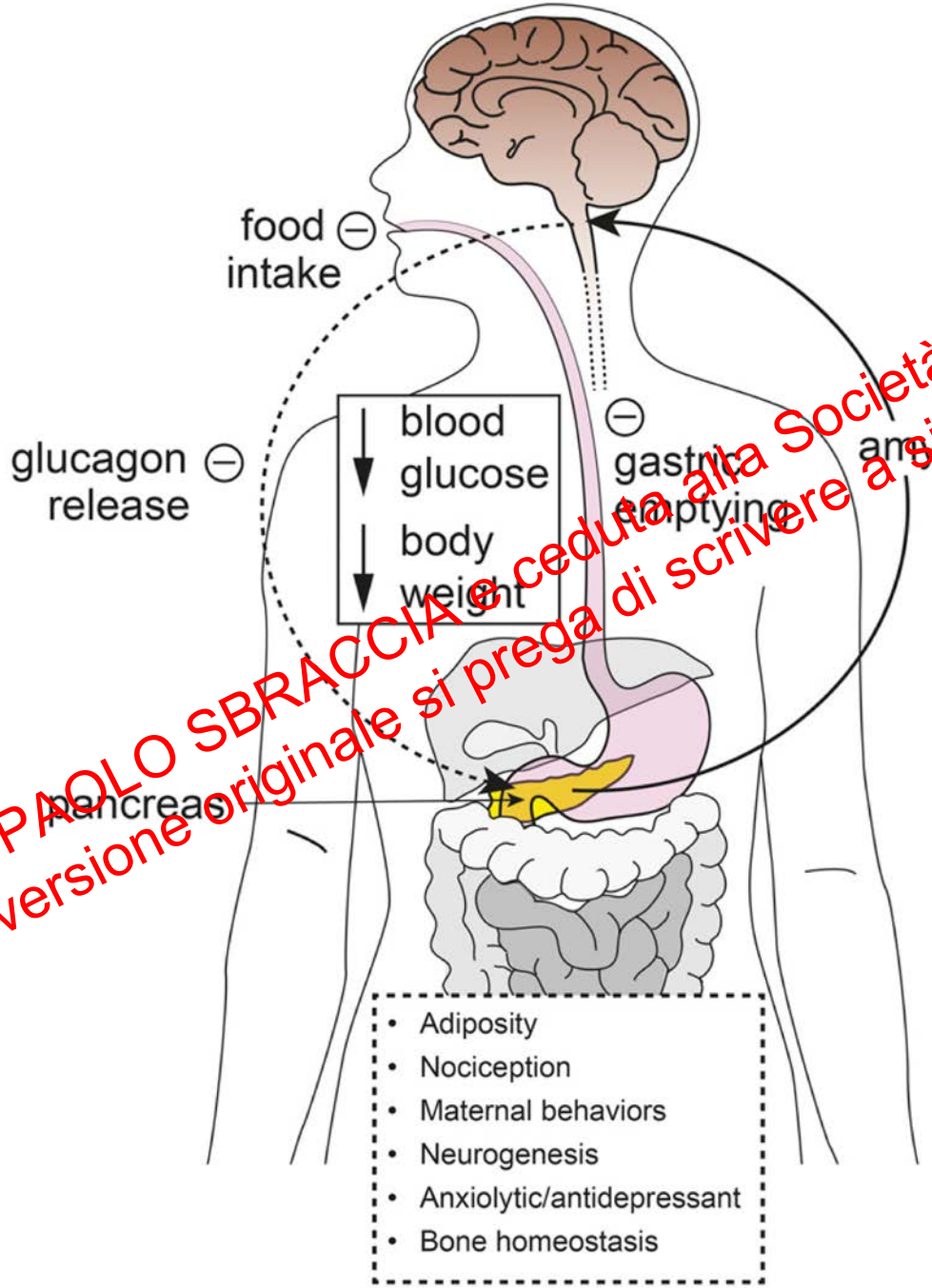
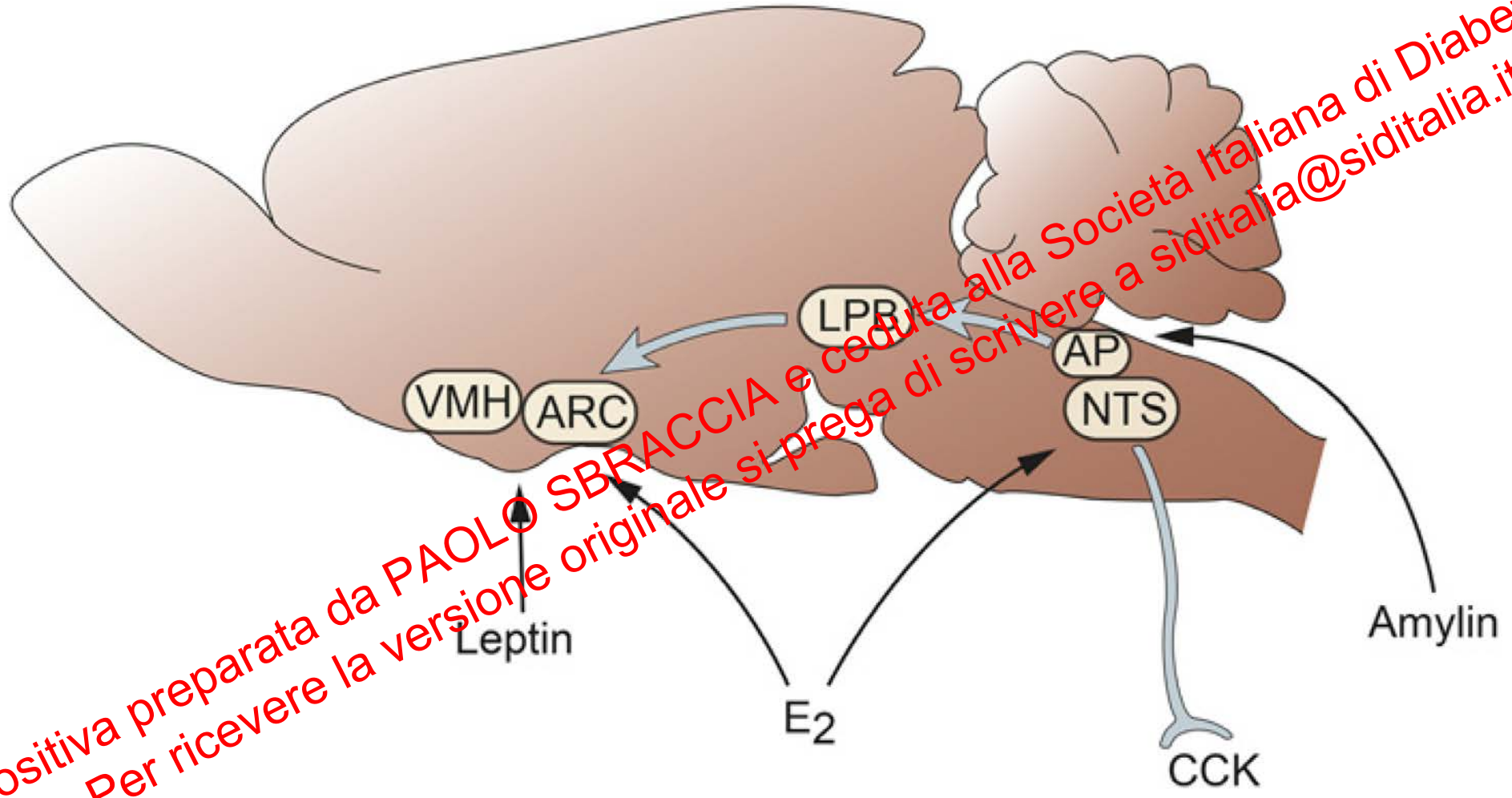
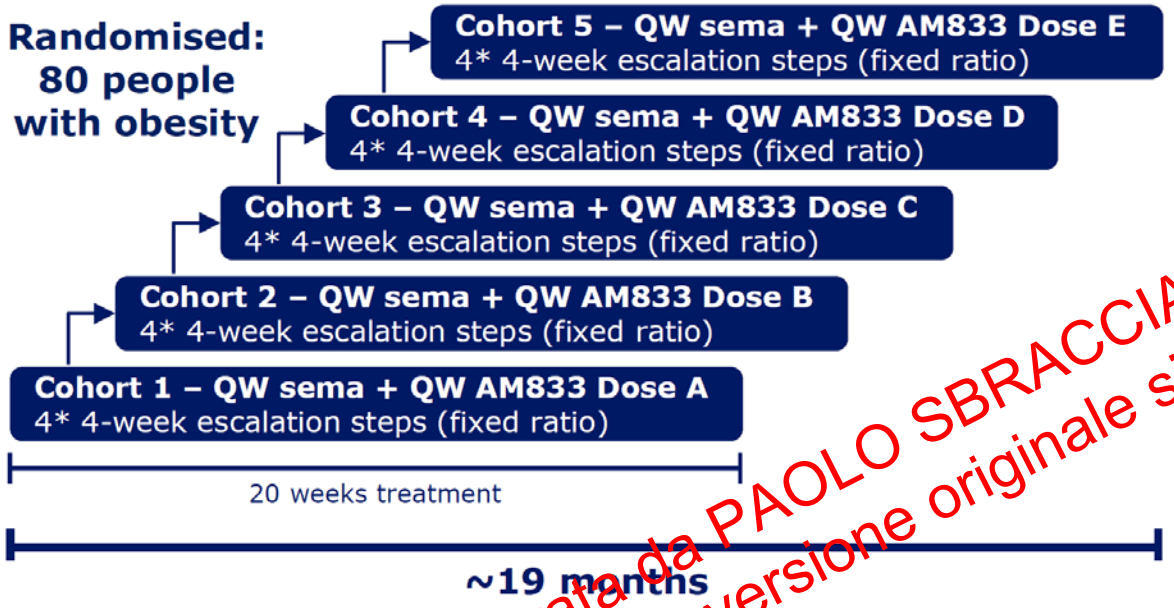




Amylin AM833 could become the next step in getting closer to the ambition of >20% weight loss

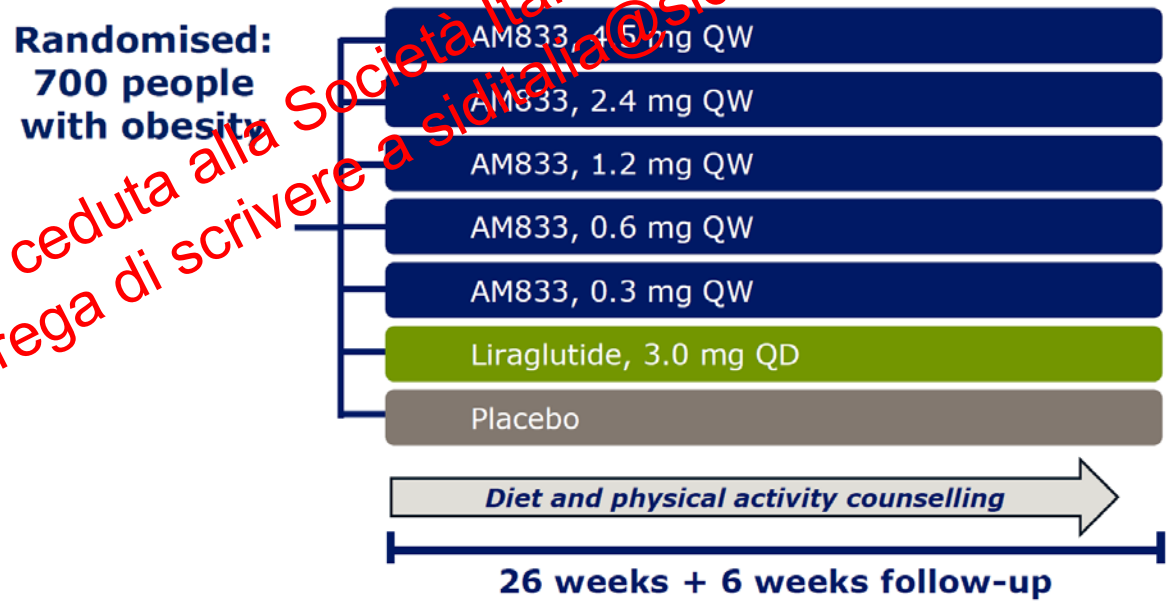
Phase 1b amylin and semaglutide combination multiple dose trial



Trial objective

To assess the safety, tolerability and PK properties, and to explore PD effects of multiple subcutaneous doses of amylin AM833 initiated simultaneously with semaglutide in people with overweight or obesity (BMI 27-39.9 kg/m2)

Phase 2 dose finding trial



Trial rationale

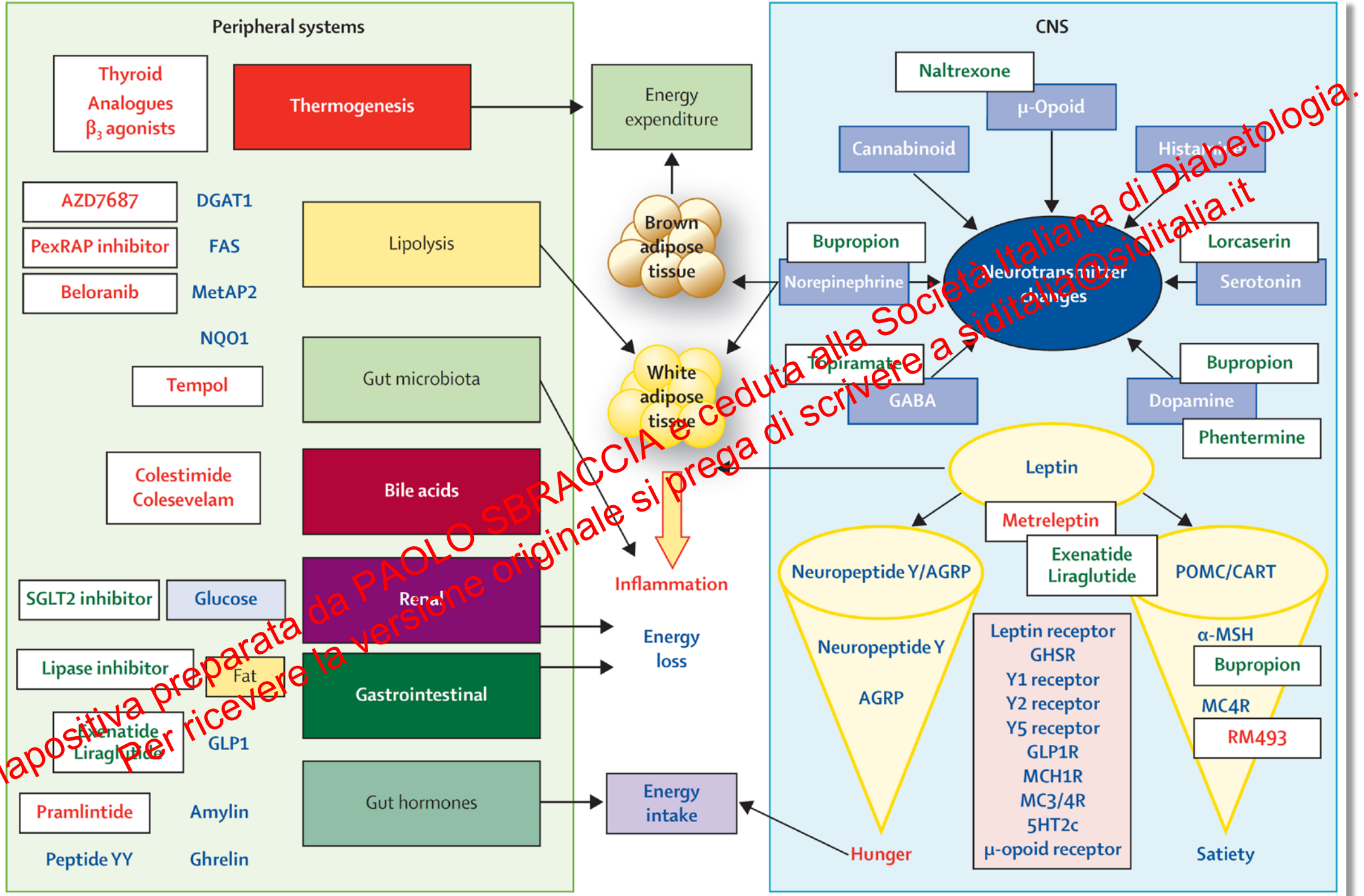
To find optimal dose of sc. administered amylin AM833 QW for weight loss in people being overweight or with obesity (BMI 27-39.9 kg/m2)

Primary endpoint

Change from baseline to week 26 in body weight (%)

Trial initiation: Q1 2019

QW: once-weekly; sema: semaglutide; sc: subcutaneous



POTREMMO PUNTARE ANCORA DI PIÙ SUL CALO PONDERALE!

T2 Diabetes: treat to target

Obesity: % Reduction in prevalence!