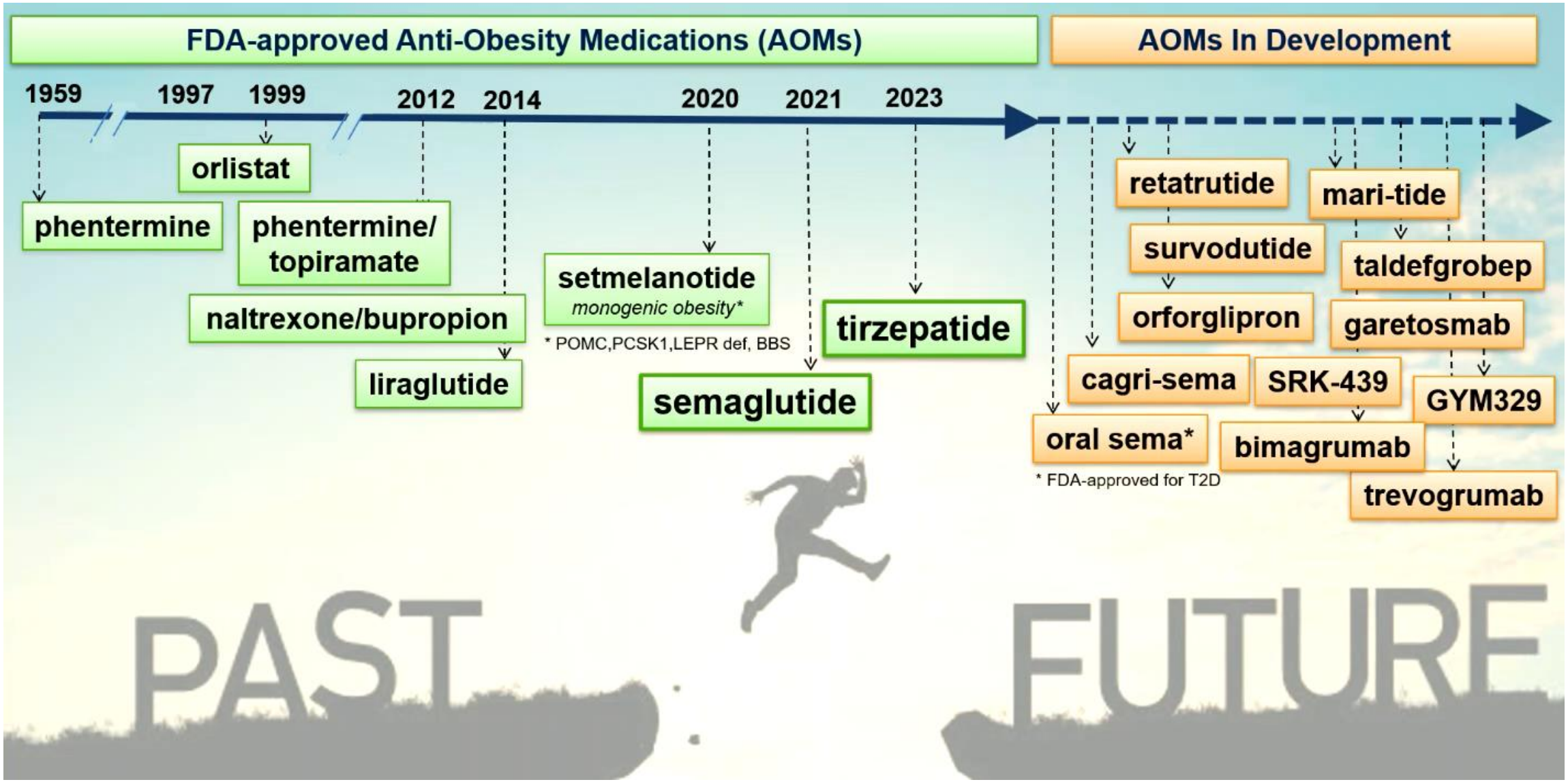
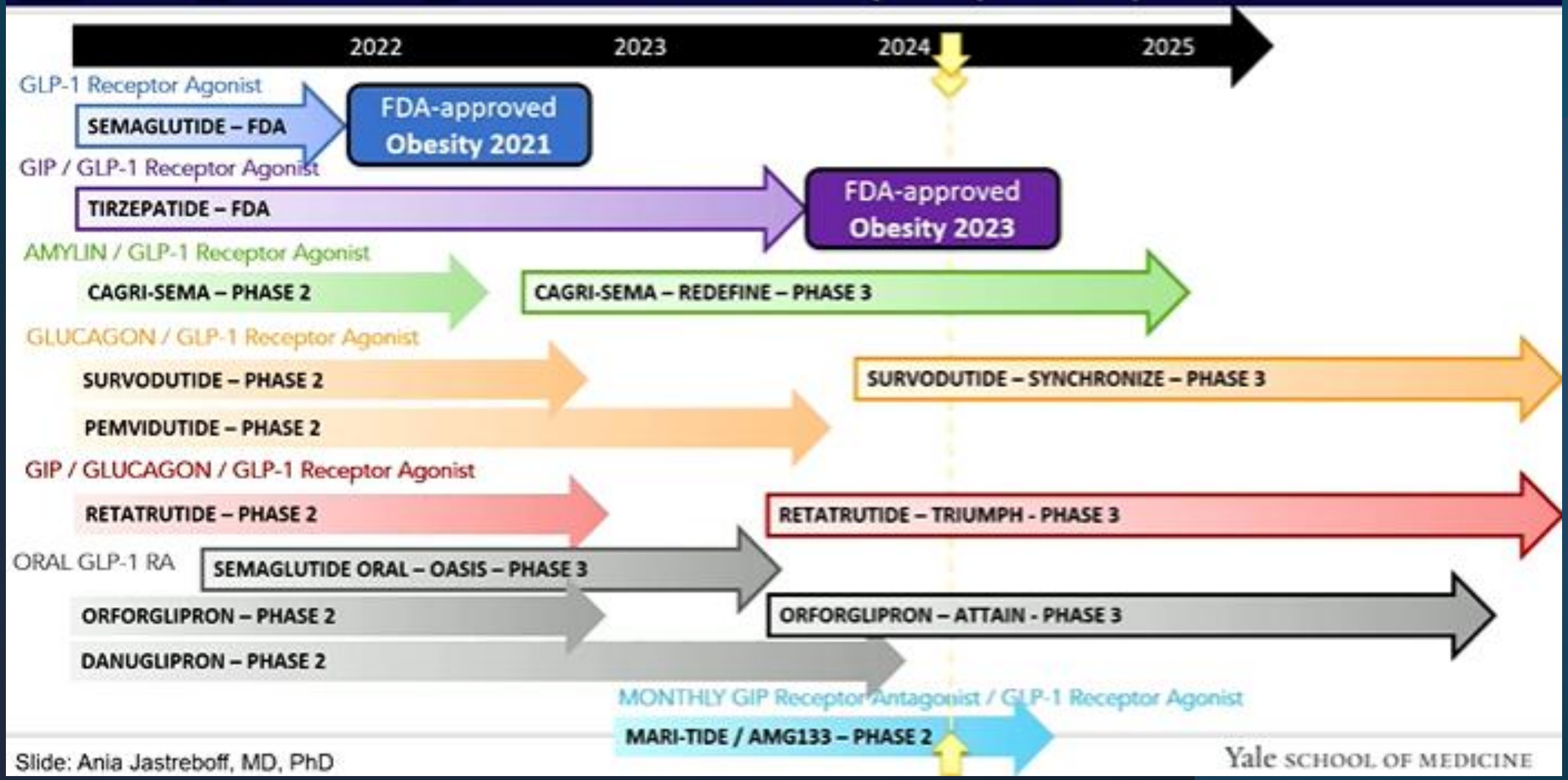
¿Qué más nos va a aportar el futuro?.

Dra. Olga González Albarrán. Endocrinología. Hospital Universitario Gregorio Marañón.


FDA-approved Anti-Obesity Medications (AOMs)
AOMs In Development
1959
1997
1999
2012
2014
2020
2021
2023
orlistat
phentermine
phentermine/ topiramate
naltrexone/bupropion
liraglutide
setmelanotide
monogenic obesity*
* POMC,PCSK1,LEPR def, BBS
semaglutide
tirzepatide
retatrutide
mari-tide
survodutide
taldefgrobep
orforglipron
garetosmab
cagri-sema
SRK-439
GYM329
oral sema*
bimagrumab
* FDA-approved for T2D
trevogrumab
PAST
FUTURE

Anti-Obesity Medications in the Pipeline
Nutrient-Stimulated Hormone-based therapies (NuSHs)



Slide: Ania Jastreboff, MD, PhD

Yale SCHOOL OF MEDICINE

GLP1RA

Table 1: GLP1RAs currently on the market or in clinical development

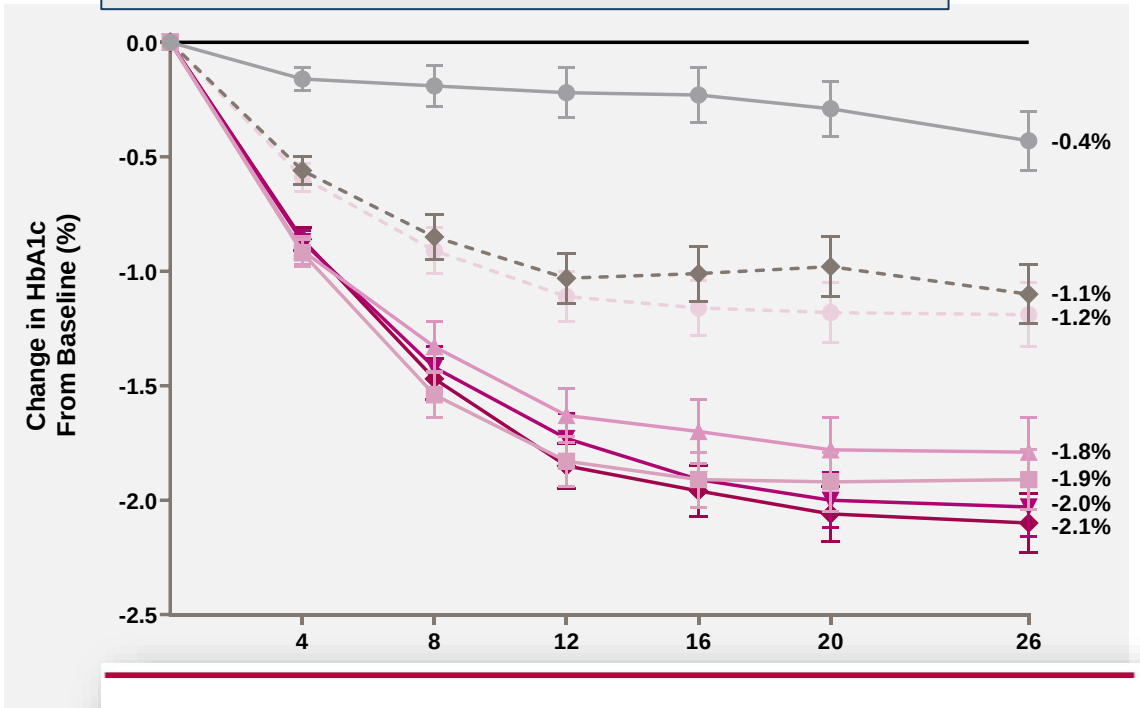
Name	Company	Class	Highest development phase	Current status of the ongoing trials/References
Liraglutide (Saxenda)	Novo Nordisk	GLP1RA	FDA/EMA approved	• Based on the results of SCALE trials,[11-15] the FDA authorized the use of Liraglutide 3.0 mg in December 2014, and the EMA followed suit in March 2015. This medication, marketed as Saxenda by Novo Nordisk, is used for chronic weight management in IWO or overweight.
Semaglutide (Wegovy)	Novo Nordisk	GLP1RA	FDA/EMA approved	• Based on the results of STEP trials,[18-22] the FDA authorized the use of Semaglutide 2.4 mg in June 2021, and the EMA followed suit in January 2022. This medication, marketed as Wegovy by Novo Nordisk, is used for chronic weight management in IWO or overweight.
Semaglutide (Rybelsus)	Novo Nordisk	Oral GLP1RA	Phase III	• The OASIS trials are currently investigating higher doses (25 mg and 50 mg daily) of oral Semaglutide for obesity management in IWO or overweight but without T2DM. • The OASIS 1 trial demonstrated that oral Semaglutide 50 mg led to a significant weight loss in participants with overweight or obesity, as reported on 22nd May 2023. At week 68, oral Semaglutide 50 mg users achieved a body weight reduction of -15.1% compared to -2.4% in the placebo group (estimated treatment difference: 1 2.7%, 95% CI: −14.2% to −11.3%; $P<0{\cdot}0001$).[26]
Danuglipron (PF-06882961)	Pfizer	Small-molecule GLP1RA (Oral)	Phase IIb	• In a phase I study, 98 participants with T2DM who were taking metformin were randomly assigned to receive different doses of Danuglipron or placebo for 28 days. The study evaluated the drug's safety, tolerability, and pharmacokinetic and pharmacodynamic profiles. Adverse effects such as nausea, dyspepsia, and vomiting were reported, but overall, the drug was well tolerated and showed dose-dependent improvements in glycaemic control. Notably, the 70 mg twice daily dose of Danuglipron resulted in a weight reduction of 4.4 kg at day 28 compared to 1.8 kg for placebo, with a lower incidence of adverse events.[27] • Further clinical development of the drug for the treatment of T2DM and obesity is currently underway. In January 2021, Pfizer initiated a phase IIb trial to evaluate the efficacy, safety, tolerability, and pharmacokinetics of Danuglipron administration in adults with obesity (NCT04707313).
Orforglipron (LY3502970)	Eli Lilly and Company	Non-peptide GLP1RA	Phase III Attain-2 trial (Active and recruiting)	• A phase II study was a 36-week, multi-centre, double-blind RCT comparing the efficacy and safety of Orforglipron (12 mg, 24 mg, 36 mg, or 45 mg) to placebo in IWO or overweight with at least one co-morbidity, excluding T2DM. At the 26-week primary endpoint, different doses of Orforglipron exhibited significant and dose-dependent reductions in body weight. The weight loss ranged from 8.6% to 12.6% (9.0–13.3 kg) compared to 2.0% (2.1 kg) for placebo. By the 36-week mark, individuals taking Orforglipron experienced further decreases in body weight, with reductions ranging from 9.4% to 14.7% (9.8–15.4 kg) compared to 2.3% (2.4 kg) for placebo.[28] • Eli Lilly and Company then launched the phase III Attain-2 trial (NCT05872620).
Dapiglutide	Zealand Pharma	Long-acting GLP1R/GLP2R dual agonist	Phase II (obesity) Phase I (Short bowel syndrome)	• Phase II DREAM trial to assess the effectiveness of once-weekly SC of 4 mg and 6 mg Dapiglutide compared to a placebo over a 12-week treatment period for managing obesity (NCT05788601).

Orforglipron: GLP1RA Oral

La vida media de 29-49h apoya una dosis diaria, sin restricciones de comida y agua

Diabetes tipo 2

Reducción de A1c a semana 26 = Hasta un 2.1%

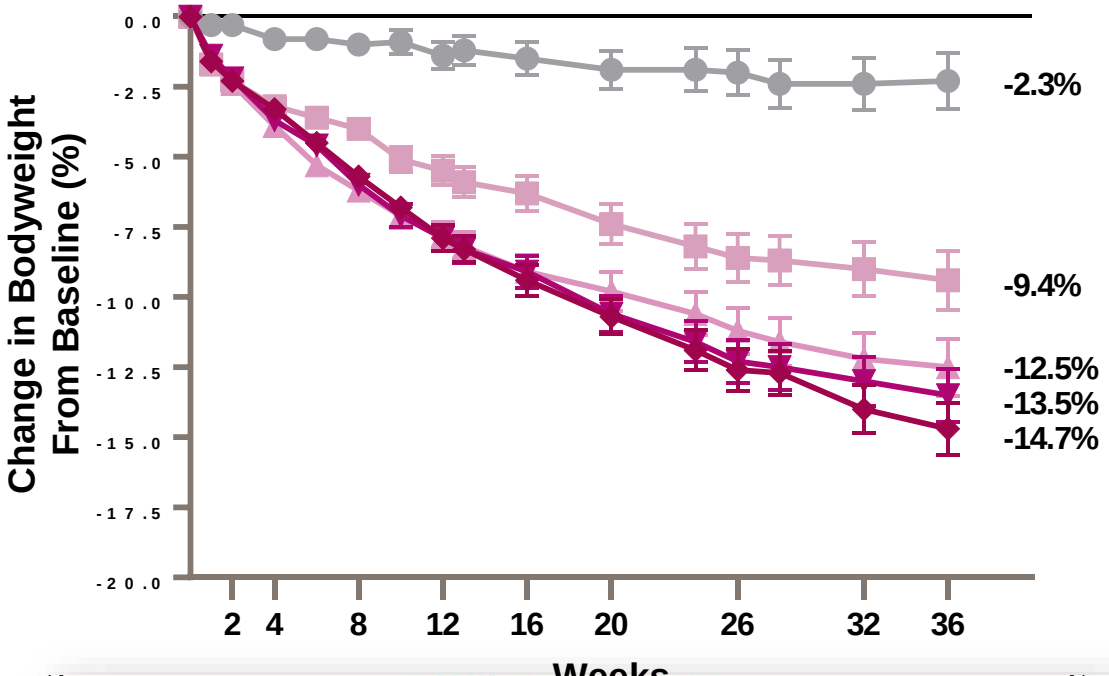


Efficacy and safety of oral orforglipron in patients with type 2 diabetes: a multicentre, randomised, dose-response, phase 2 study

Juan P Frias, Stanley Hsia, Sarah Eyde, Rong Liu, Xiaosu Ma, Manige Konig, Christof Kazda, Kieren J Mather, Axel Haupt, Edward Pratt, Deborah Robins

Obesidad

Reducción de peso a semana 36 = Hasta un 14.7%

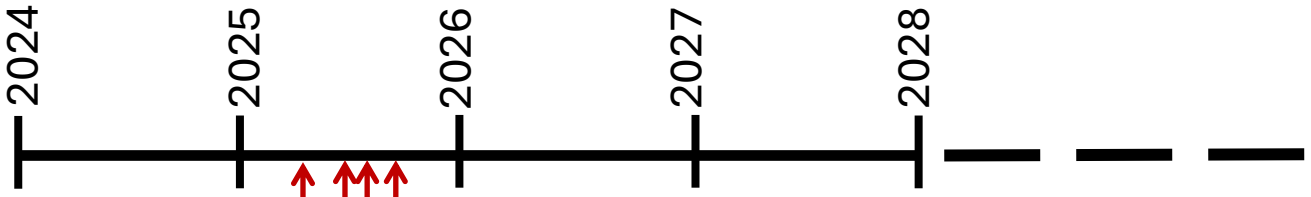


ORIGINAL ARTICI

Daily Oral GLP-1 Receptor Agonist Orforglipron for Adults with Obesity

Sean Wharton, M.D., Thomas Blevins, M.D., Lisa Connery, M.D., Julio Rosenstock, M.D., Sohini Raha, Ph.D., Rong Liu, Ph.D., Xiaosu Ma, Ph.D., Kieren J. Mather, M.D., Axel Haupt, M.D., Deborah Robins, M.S., Edward Pratt, M.D., Christof Kazda, M.D., and Manige Konig, M.D., Ph.D., for the GZGI Investigators*

Programa clínico Fase 3 con Orforglipron



ACHIEVE-1
Estudio con Orforglipron (LY3502970) en participantes adultos con diabetes tipo 2 y un inadecuado control glucémico únicamente con dieta y ejercicio
Abr 2025

ACHIEVE-4
Estudio con Orforglipron oral diario comparado con Insulina Glargina en participantes con diabetes tipo 2 y obesidad o sobrepeso con elevado riesgo cardiovascular
Abr 2025

ACHIEVE-5
Estudio con Orforglipron (LY3502970) en participantes con diabetes tipo 2 y un inadecuado control glucémico con insulina glargine, con/sin metformina y/o inhibidores de SGLT-2
Abr 2025

ATTAIN-2
Estudio para investigar la eficacia y seguridad de Orforglipron oral diario comparado con placebo en peso corporal en participantes adultos con obesidad o sobrepeso y diabetes tipo 2
Junio 2025

ACHIEVE-3
Estudio con Orforglipron (LY3502970) comparado con Semaglutida en participantes con diabetes tipo 2 y un inadecuado control glucémico con metformina
Jul 2025

ATTAIN-1
Estudio para investigar la eficacia y seguridad de Orforglipron oral diario comparado con placebo en participantes adultos con obesidad o sobrepeso con comorbiliades relacionadas
Sept 2025

ACHIEVE 1 - NCT05971940
ACHIEVE-3 – NCT06045221
ACHIEVE-4 – NCT05803421
ACHIEVE-5 – NCT06109311
ATTAIN-1 - NCT05869903
ATTAIN-2 - NCT05872620

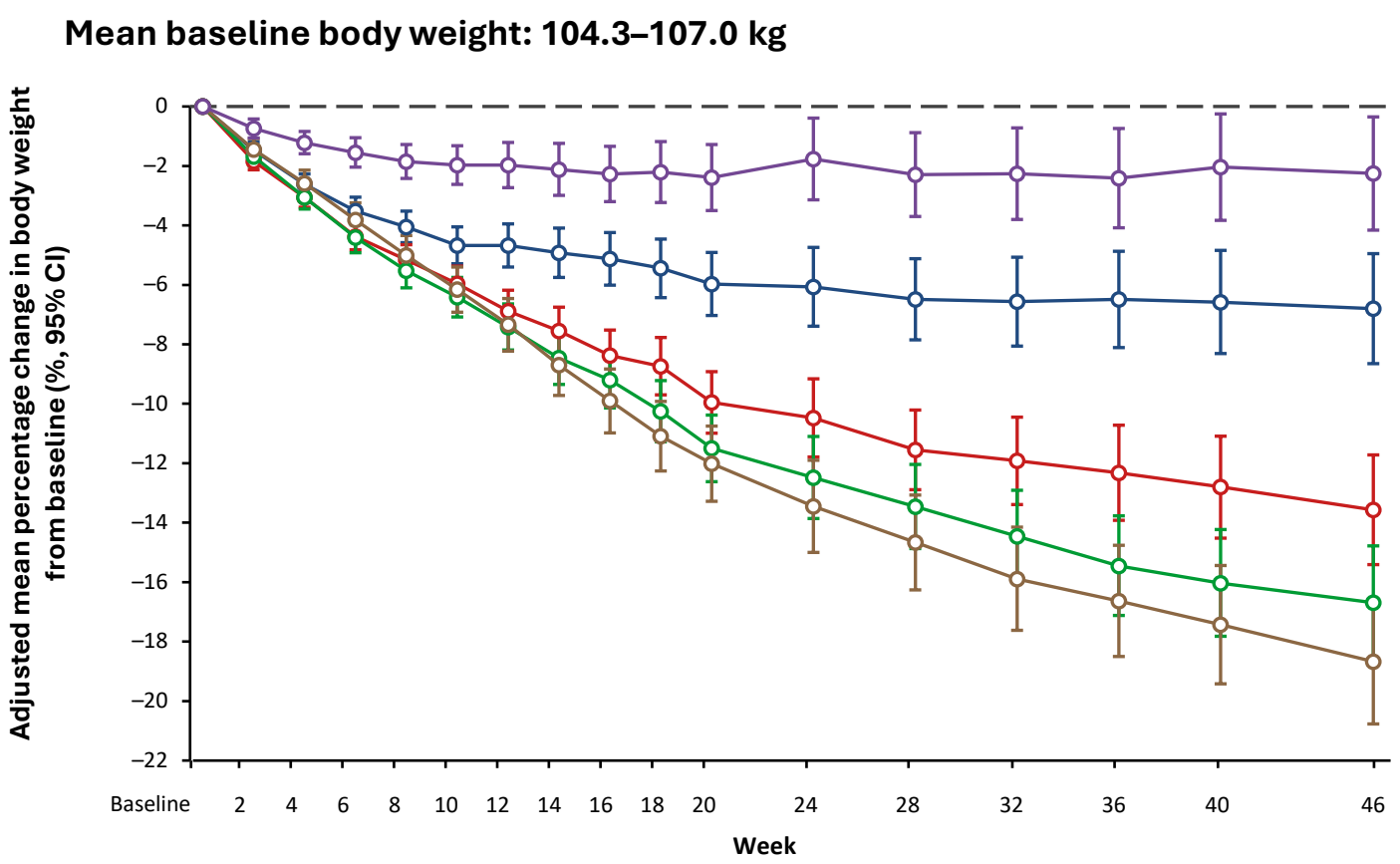
DUALES: GLP1R/GCGR

Table 4: GLP1R/GCGR in clinical development

Name	Company	Class	Highest development phase	Current status of the ongoing trials/References
Cotadutide (MEDI0382)	AstraZeneca/ Medimmune	GLP1R/GCGR dual agonist	Phase II (T2DM/Obesity) Phase II (T2DM) Phase II (T2DM)	• The daily injectable GLP1R/GCGR dual agonist, Cotadutide (MEDI0382), was being developed by AstraZeneca to treat T2DM, obesity, NAFLD, and NASH. Cotadutide exhibited a balanced agonist effect on the GLP1R and GCGR with a ratio of approximately 5:1 GLP1R to GCGR activity.[63] • Clinical trials were conducted in multiple countries and reached phase IIb/III in non-cirrhotic NASH with fibrosis (PROXYMO-ADV, NCT05364931). • Additionally, Cotadudite significantly improved glycaemic control and weight reduction among IWO and T2DM in a 54-week-phase IIb study.[64] • Due to strategic pipeline considerations, the development of Cotadutide has been discontinued in favour of focusing on AZD9550, a once-weekly injectable GLP1RA/GCGR. AstraZeneca will shift its focus to the ever-growing diabetes and obesity market due to the increased utilization of GLP1RA mono-agonists and dual agonists for both indications.[65] AstraZeneca's decision is surprising as NASH has no approved therapies. Other GLP1RAs being developed for NASH include Semaglutide and Tirzepatide.[66] Data suggests that dual agonists such as Cotadutide may be more effective in NASH than mono-agonists.
Survodutide (BI456906)	Boehringer Ingelheim/ Zeeland Pharma	GLP1R/GCGR dual agonist	Phase III (obesity; NASH; T2DM)	• The once-weekly long-acting GLP1R/GCGR dual agonist, Survodutide, is also undergoing development by Boehringer Ingelheim and Zealand Pharma. Initially focused on NASH, there is now a shift in attention towards obesity and its co-morbidities.[67] • Phase 1 studies of Survodutide showed a placebo-adjusted average body weight reduction of 13.8% ± 1.6% among participants in the DS7 group of the MRD study.[68] • In its phase 2 trial involving the obese non-diabetic population, Survodutide demonstrated a weight loss of 14.9% over 46 weeks and reached up to 18.7% in individuals who reached and stayed on the maximum dose of 4.8 mg compared to 2.0% with placebo (NCT04667377).[69] • These "encouraging data" support further study of Survodutide for weight reduction in larger Phase III trials. SYNCHRONIZE-1 (NCT06066515) and SYNCHRONIZE-2 (NCT06066528) are Phase III studies investigating Survodutide in IWO or overweight without T2DM and with T2DM, respectively.[69] • Survodutide has received FDA fast-track designation for adults with NASH.[69]
Mazdutide (IBI-362; LY-3305677; OXM-3)	Eli Lilly and Company; Innovent Biologics	Long-acting OXM analogue (GLP1R/GCGR dual agonist)	Phase III; ongoing (obesity) Phase III; ongoing (Diabetes) Phase II (Diabetes)	• Innovent Biologics conducted a phase I trial to evaluate the efficacy and safety of Mazdutide dosed up to 9 mg and 10 mg. High-dose Mazdutide demonstrated promising results in a 12-week trial, showing significant body weight loss. At week 12, the mean percent change in body weight from baseline was −11.7% in the Mazdutide 9 mg cohort compared to −1.8% in the placebo group (estimated treatment difference of −9.8%; 95% CI: −14.4% to −5.3%; *P*=0.0002). At week 16, the mean percent change in body weight from baseline was -9.5% in the Mazdutide 10 mg cohort compared to -3.3% in the placebo group (estimated treatment difference of −6.2%; 95% CI: −11.5% to −0.9%; *P*=0.024). This suggests its potential as a treatment for moderate-to-severe obesity.[70]

Survodutide: Dual GCGR/GLP-1R agonists

Survodutide treatment (actual) dose-dependently reduced participant body weight up to 18.7% over 46 weeks

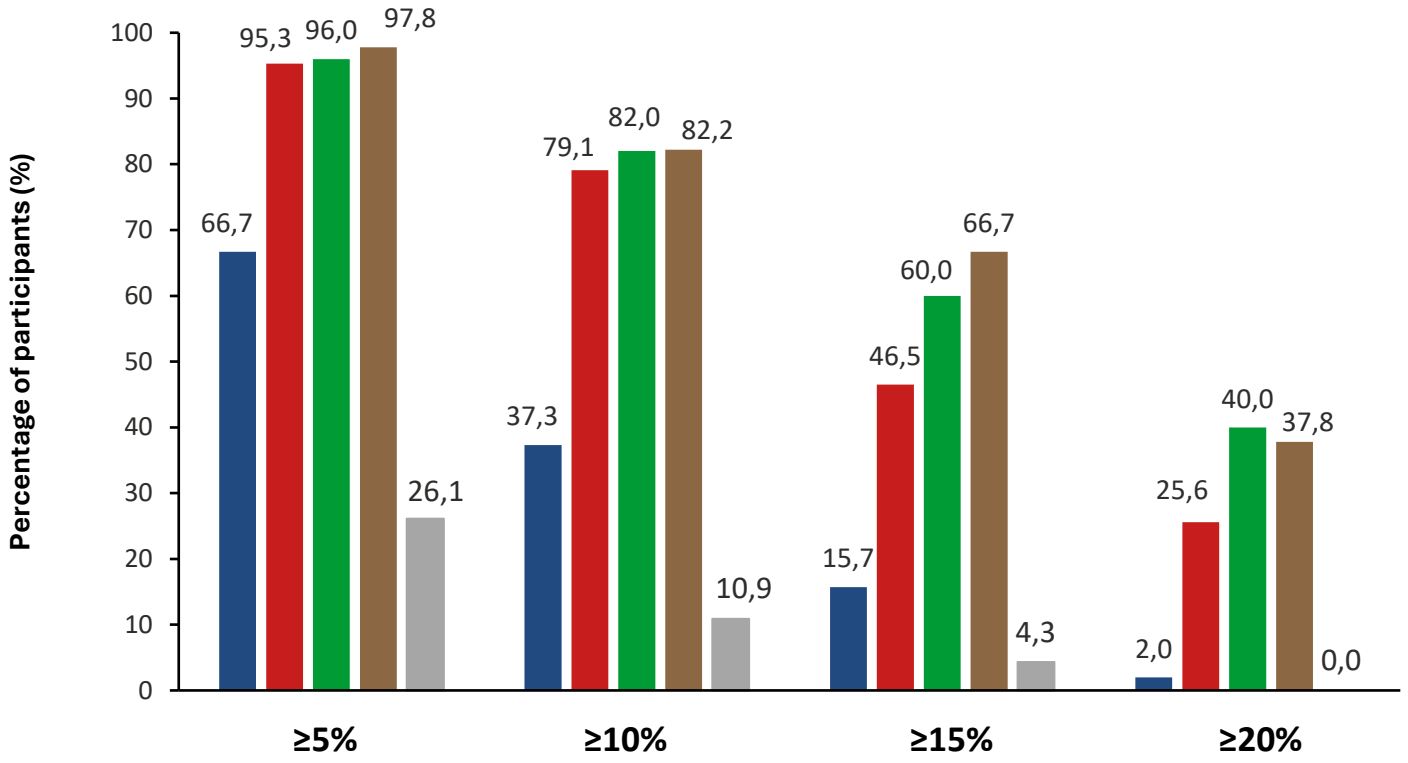


Mean relative body weight change at Week 46 (%)	
Placebo (n=76)	**−2.3**
Survodutide 0.6 mg QW (n=88)	**−6.8**
Survodutide 2.4 mg QW (n=92)	**−13.6**
Survodutide 3.6 mg QW (n=71)	**−16.7**
Survodutide 4.8 mg QW (n=54)	**−18.7**

Actual treatment

le Roux CW, et al. Lancet Diabetes Endocrinol 2024;12:162–173

Up to 40% of participants (actual treatment) achieved ≥20% body weight reduction with survodutide treatment at Week 46



Actual treatment

le Roux CW, et al. Lancet Diabetes Endocrinol 2024;12:162–173

The most common AEs were gastrointestinal, which was in line with expectations based on the mode of action

AEs, n (%)	Survodutide 0.3 mg QW (n=50)	Survodutide 0.9 mg QW (n=50)	Survodutide 1.8 mg QW (n=52)	Survodutide 2.7 mg QW (n=50)	Survodutide 1.2 mg BIW (n=51)	Survodutide 1.8 mg BIW (n=49)	Semaglutide 1.0 mg QW (n=50)*	Placebo (n=59)	Total survodutide (n=302)
Any TEAE	33 (66.0)	38 (76.0)	42 (80.8)	41 (82.0)	39 (76.5)	42 (85.7)	26 (52.0)	31 (52.5)	235 (77.8)
Investigator-defined treatment-related AEs	25 (50.0)	26 (52.0)	33 (63.5)	29 (58.0)	28 (54.9)	36 (73.5)	19 (38.0)	13 (22.0)	177 (58.6)
Nausea	10 (20.0)	13 (26.0)	24 (46.2)	20 (40.0)	14 (27.5)	22 (44.9)	6 (12.0)	5 (8.5)	103 (34.1)
Vomiting	6 (12.0)	7 (14.0)	12 (23.1)	13 (26.0)	6 (11.8)	10 (20.4)	2 (4.0)	1 (1.7)	54 (17.9)
Diarrhoea	11 (22.0)	5 (10.0)	8 (15.4)	7 (14.0)	8 (15.7)	9 (18.4)	4 (8.0)	5 (8.5)	48 (15.9)

In participants receiving survodutide, 56 **(74%)** of 76 discontinuations due to AEs occurred during rapid dose escalation

Treatment-related serious AEs†	1 (2.0)	1 (2.0)	1 (1.9)	1 (2.0)	0	0	0	0	4 (1.3)
AEs leading to discontinuation	5 (10.0)	5 (10.0)	11 (21.2)	15 (30.0)	4 (7.8)	8 (16.3)	2 (4.0)	3 (5.1)	48 (15.9)

NCT04153929: Phase II overweight/obesity +T2D.

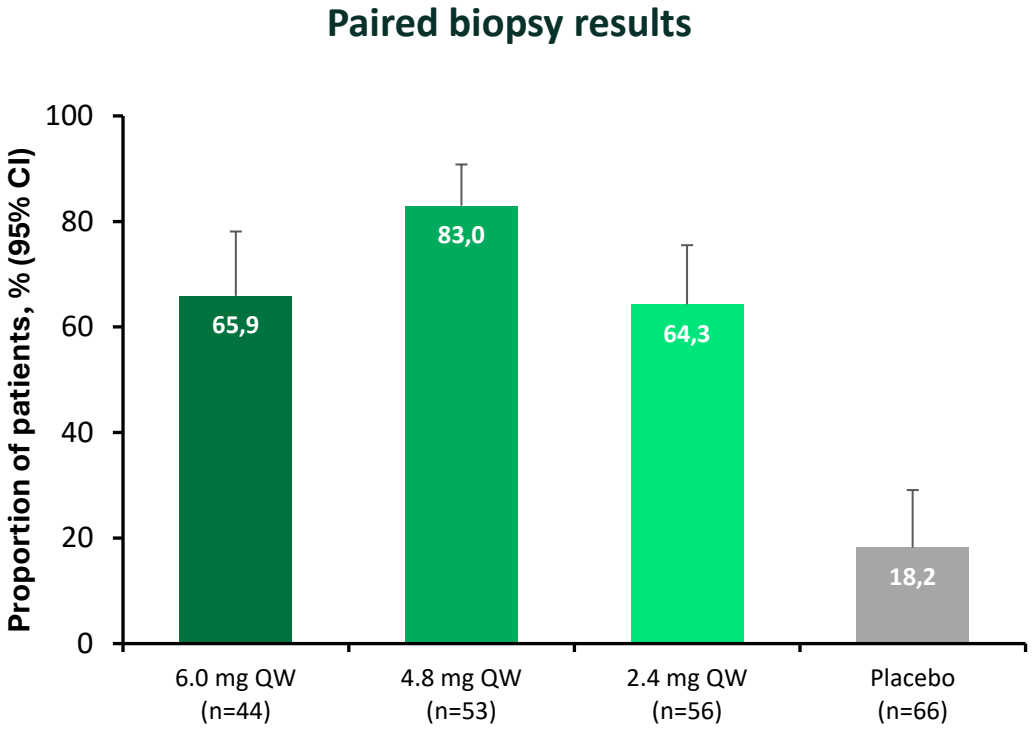
Survodutide is an investigational agent and has not been approved by regulatory agencies. The efficacy and safety of survodutide is still under investigation.

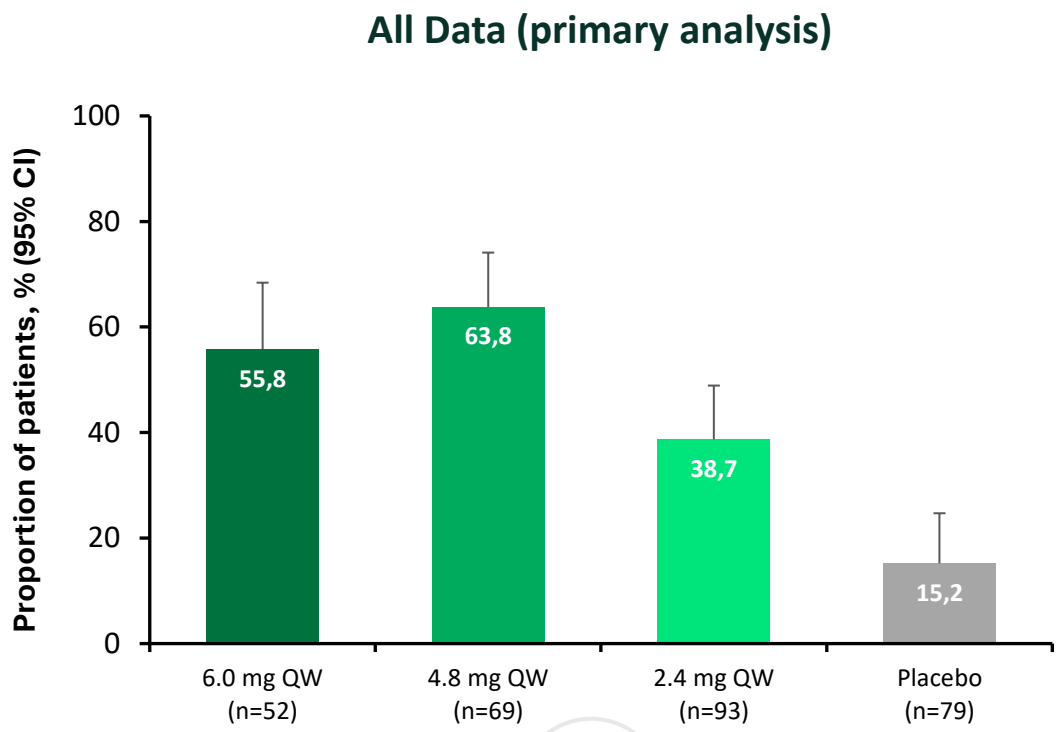
*Semaglutide is open label; †Abdominal pain, vomiting (survodutide 0.3 mg QW); irritable bowel syndrome, cellulitis, autoimmune disorder, mouth ulceration, pharyngeal ulceration (survodutide 0.9 mg QW); IIIrd nerve paralysis, paraparesis, dehydration (survodutide 1.8 mg QW); diarrhoea, viraemia (survodutide 2.7 mg QW); athralgia, back pain(survodutide 1.2 mg BIW).

AE, adverse event; BIW, twice weekly; MASH, metabolic dysfunction-associated steatohepatitis; QW, once weekly; TEAE, treatment-emergent adverse event.

Blüher M, et al. Diabetologia 2024;67:470–482.

Improvement in MASH with no worsening in fibrosis was observed in up to 83.0%* of participants that received survodutide (F1–F3 population)[1,2]



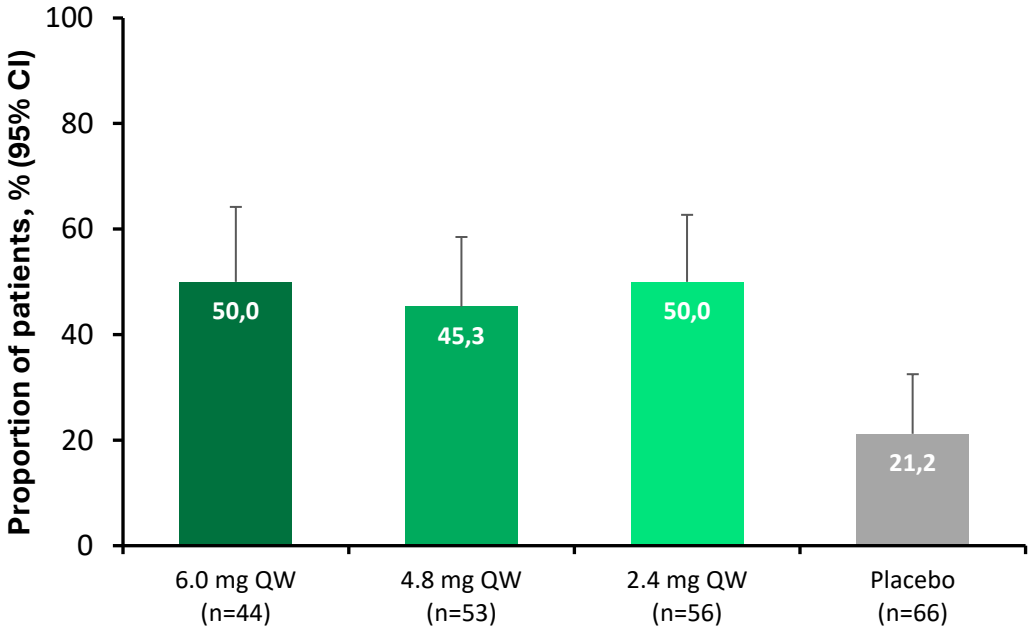


Actual treatment

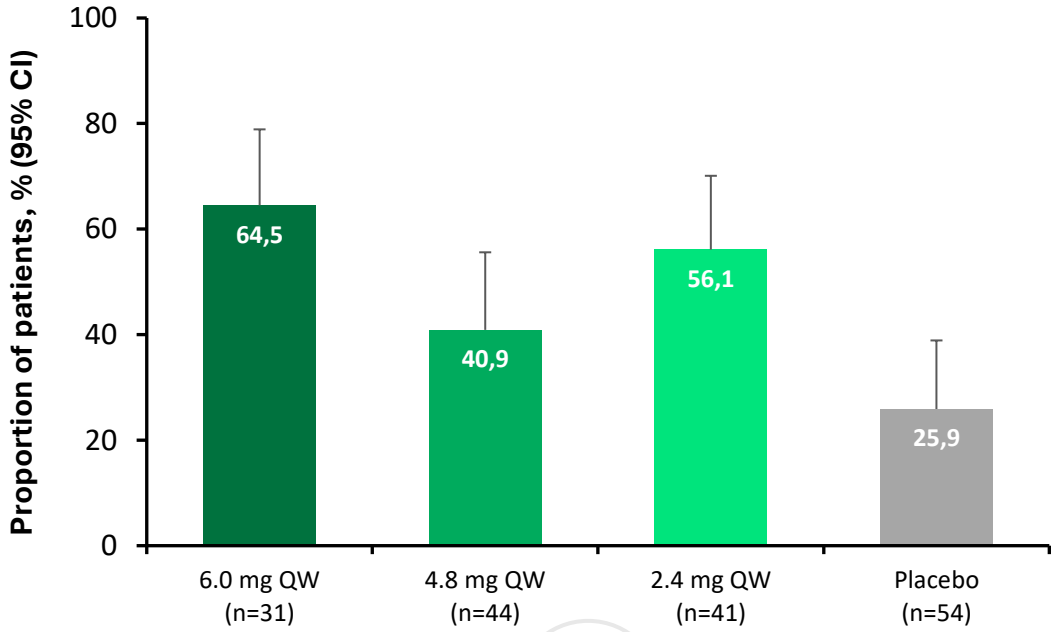
1. Sanyal AJ, et al. N Engl J Med 2024;391:311-319 (Supplemental). 2. Sanyal AJ, et al. EASL 2024; presentation GS-006..

Improvement in liver fibrosis with no worsening in MASH was observed in up to 64.5%* of participants that received survodutide (F2/F3 population)[1,2]

Paired biopsy results (F1–F3)*



Paired biopsy results (F2/F3)



Actual treatment

1. Sanyal AJ, et al. N Engl J Med 2024;391:311-319 (Supplemental). 2. Sanyal AJ, et al. EASL 2024; presentation GS-006..

Phase 3 programmes will investigate survodutide in people living with overweight or obesity, MASH and other CRM conditions

SYNCHRONIZE™ Phase 3 programme

SYNCHRONIZE™-1:[1]
- People living with **overweight or obesity without T2D**

SYNCHRONIZE™-2:[2]
- People living with **overweight or obesity and T2D**

SYNCHRONIZE™-CVOT:[3]
- People living with **overweight or obesity** with **CVD/CKD or risk factors**

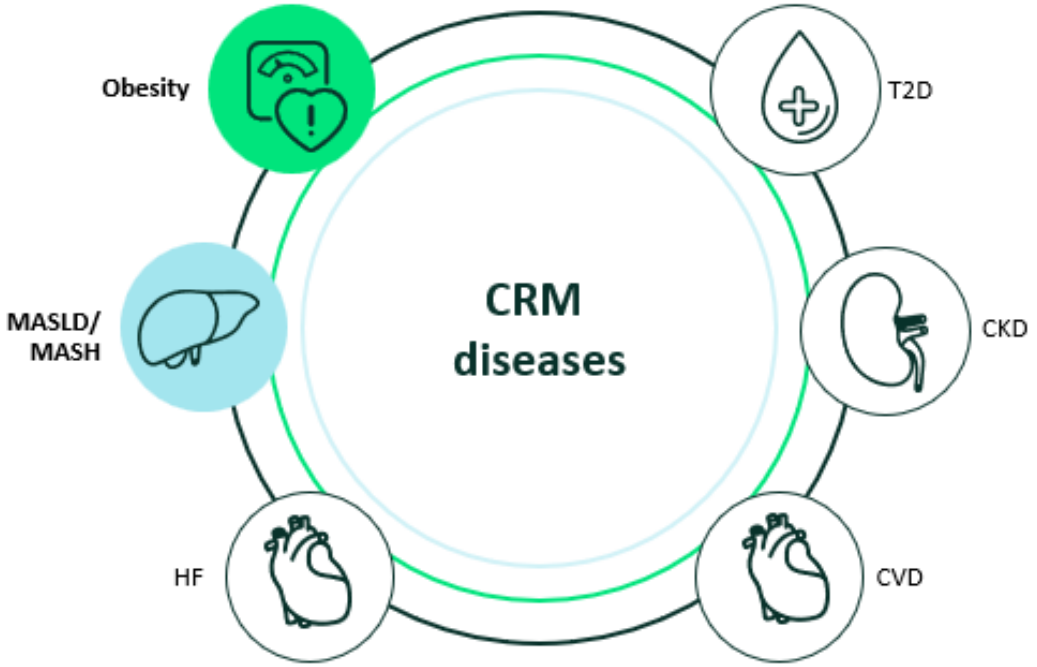
SYNCHRONIZE™-MASLD:[4,7]
- People living with **overweight or obesity** with **presumed or confirmed MASH**

Standalone trials in China and Japan (SYNCHRONIZE-CN and SYNCHRONIZE-JP) are designed to meet local guidelines for registration, including BMI cutoffs[5,6]

LIVERAGE™ Phase 3 programme

LIVERAGE™:[7]
- People living with **non-cirrhotic MASH and F2–F3**

LIVERAGE™-cirrhosis:[8]
- People living with **MASH and compensated cirrhosis**



Future studies of survodutide may investigate potential benefits in people living with other CRM diseases

Survodutide is not approved for the treatment of MASH or cirrhosis. The efficacy and safety of survodutide are still under investigation.

BMI, body mass index; CKD, chronic kidney disease; CRM, cardiovascular–renal–metabolic; CVD, cardiovascular disease; CVOT, cardiovascular outcome trial; F2/F3, fibrosis stage 2 or 3; HF, heart failure; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; T2D, type 2 diabetes.

1. ClinicalTrials.gov: NCT06066515; accessed May 2024. 2. ClinicalTrials.gov: NCT06066528; accessed May 2024. 3. ClinicalTrials.gov: NCT06077864; accessed May 2024.
4. ClinicalTrials.gov: NCT06309992; accessed May 2024. 5. ClinicalTrials.gov: NCT06214741; accessed May 2024. 6. ClinicalTrials.gov: NCT06176365; accessed May 2024.
7. ClinicalTrials.gov: NCT06632444; accessed Oct 2024. 8. ClinicalTrials.gov: NCT06632457; accessed Oct 2024.

DUALES: GLP1R/AMILINA

Table 2: AMYRAs and DACRAs in clinical development

Name	Company	Class	Highest development phase	Current status of the ongoing trials/References
Cagrilintide	Novo Nordisk	Long-acting AMYRA	Phase II (obesity)	• In a 26-week study, once-weekly SC injections of Cagrilintide in IWO or overweight resulted in significant weight loss with all doses of Cagrilintide (0.3–4.5 mg, 6.0%–10.8%) versus placebo (3.0%; placebo-subtracted weight reduction 3.0%–7.8%; $P<0.001$). Cagrilintide 4.5 mg resulted in greater weight reduction compared to Liraglutide 3.0 mg (10.8% vs 9.0%; estimated treatment difference: 1.8%, $P=0.03$).[35]
CagriSema	Novo Nordisk	AMYRA/ GLP1RA fixed-dose combination	Phase III (obese non-diabetic; REDEFINE 1) Phase III (obese diabetic; REDEFINE 2)	• Combined with Semaglutide, Cagrilintide produced a more substantial weight reduction in IWO. • In the phase 1b trial, the CagriSema combination for 20 weeks resulted in substantial weight loss (17.1%) compared to (9.8%) with Semaglutide monotherapy; estimated treatment difference of −7.3% [95% CI: −11.2% to −3.5%] for CagriSema 2.4/2.4 vs Placebo/Semaglutide.[36] • The REDEFINE 1 trial (NCT05567796) evaluates the efficacy and safety of CagriSema SC 2.4 mg/2.4 mg once weekly in individuals with obesity or overweight, while the participants in REDEFINE 2 trial (NCT03600480) are individuals with obesity and T2DM.
Petrelintide (ZP8396)	Zealand Pharma	Long-acting AMYRA	Phase 1a (obesity)	• A first-in-human, randomized, single ascending dose trial assessing the safety, tolerability, pharmacokinetics, and pharmacodynamics of ZP8396 administered to healthy subjects demonstrated dose-dependent weight loss of up to a mean of 4.2% in ZP8396-treated individuals compared to 0.6% body weight increase from baseline in placebo-treated individuals (NCT05096598).
LY3841136	Eli Lilly and Company	Long-acting AMYRA	Phase I (obesity)	• A study to evaluate the safety, tolerability, and pharmacokinetics of LY3841136 in healthy and overweight participants (NCT05295940).
LY3541105 (DACRA QW II)	Eli Lilly and Company	DACRA (AMYR/ CALCR dual agonist)	Phase I (obesity)	• A study to evaluate the safety, tolerability, and pharmacokinetics of LY3541105 following single doses in healthy/overweight volunteers and multiple doses in overweight volunteers. DACRA produced substantial weight reduction in preclinical trials (NCT05380323).

AMYR, amylin receptor; AMYRA, amylin receptor agonist; CagriSema, Cagrilintide/Semaglutide; CALCR, calcitonin receptor; DACRA, dual amylin and calcitonin receptor agonist; GLP1RA, glucagon-like peptide-1 receptor agonist; IWO, individuals with obesity; T2DM, type-2 diabetes mellitus

CAGRILINTIDE

Amylin analogue

CAGRI-SEMA

Amylin analogue +
GLP-1 receptor agonist

Cagrilintide (Amylin analogue)
Phase 2 Trial – Participants with Obesity

Once-weekly cagrilintide for weight management in people with overweight and obesity: a multicentre, randomised, double-blind, placebo-controlled and active-controlled, dose-finding phase 2 trial

N = 706
Age = 52.3
BMI = 37.8

most frequent AEs were **gastrointestinal**

similar or lower frequency compared to liraglutide 3.0 mg

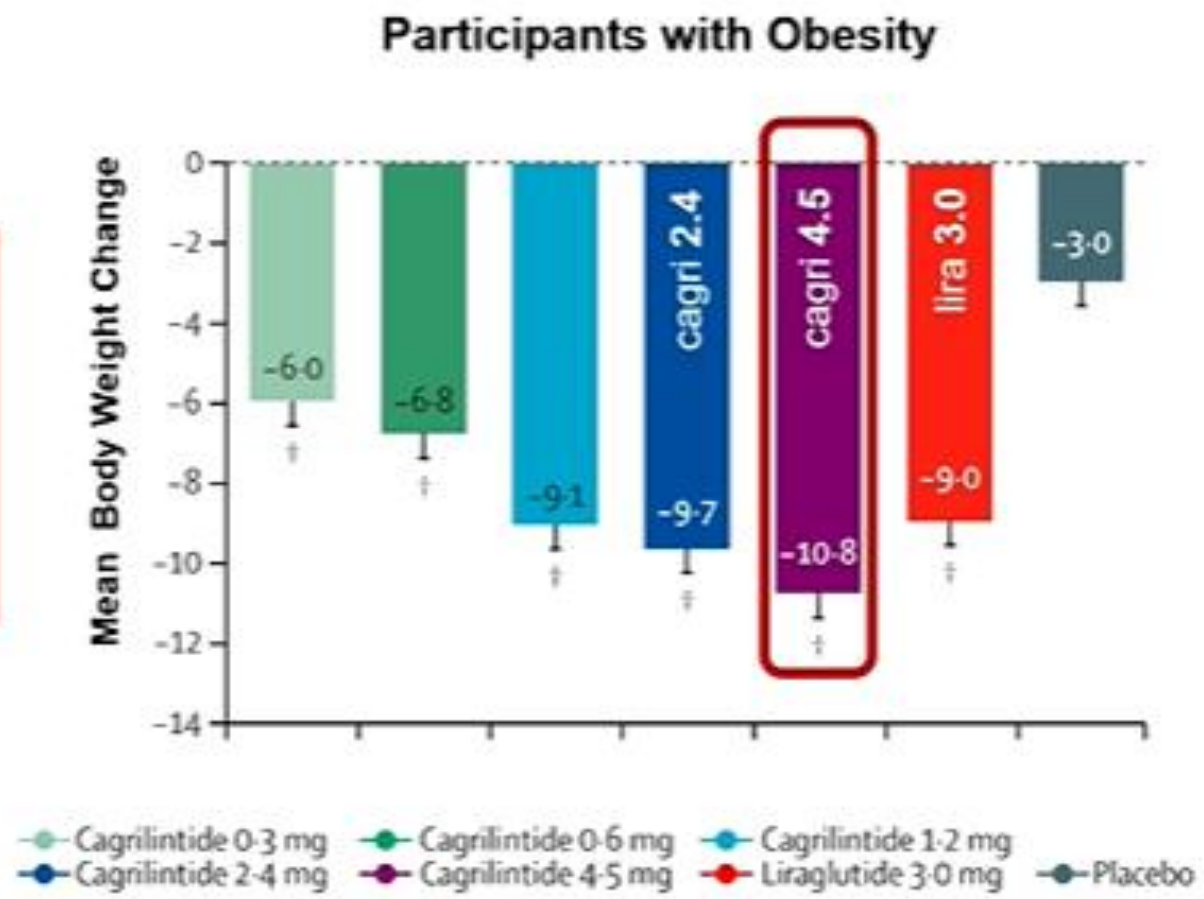
average weight reduction on treatment:

10.8%
26 weeks

Cagrilintide 4.5mg

more than half of participants lost **≥10% TBW**

Cagrilintide 4.5mg



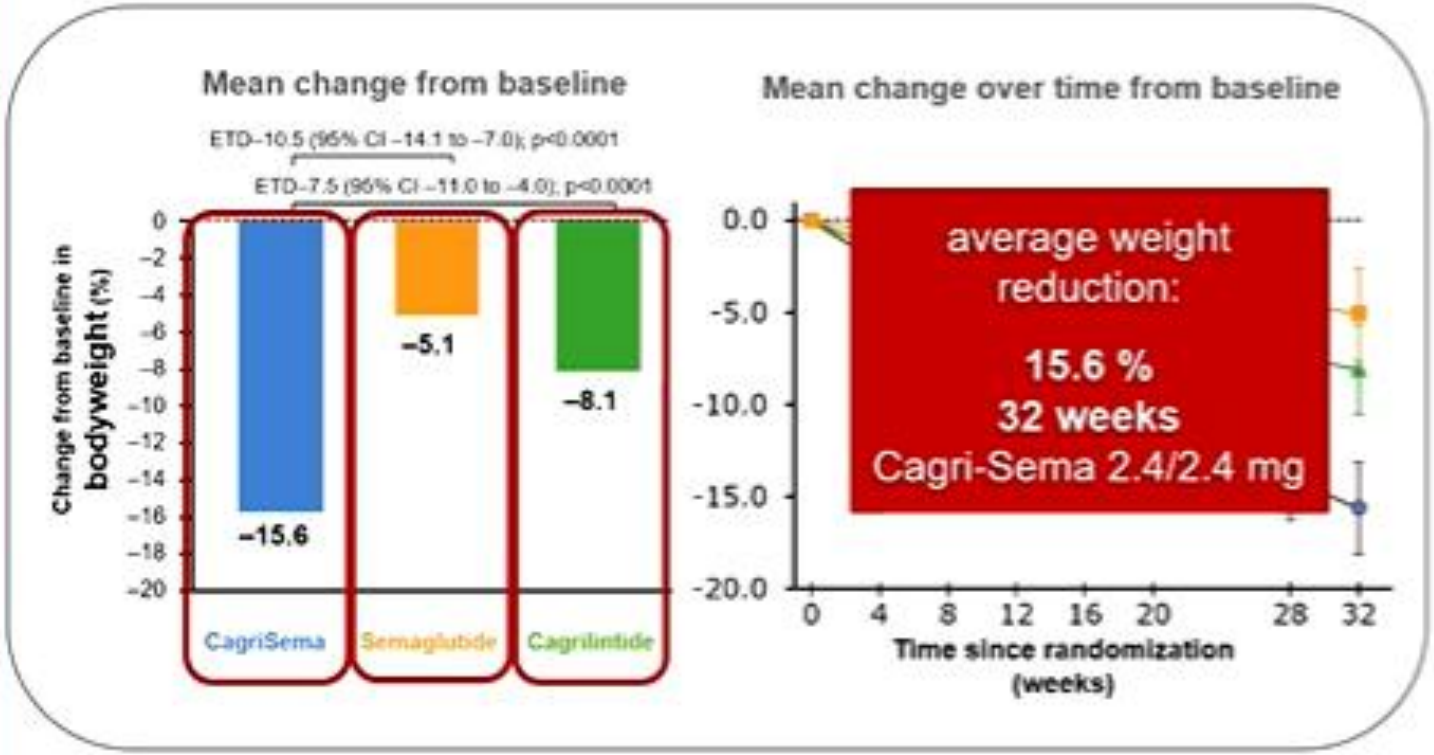
Lau D, Erichsen L, Francisco AM, *et al*. The Lancet. Dec 2021

Cagrilintide, Semaglutide, CagriSema
Phase 2 – Participants with Type 2 Diabetes

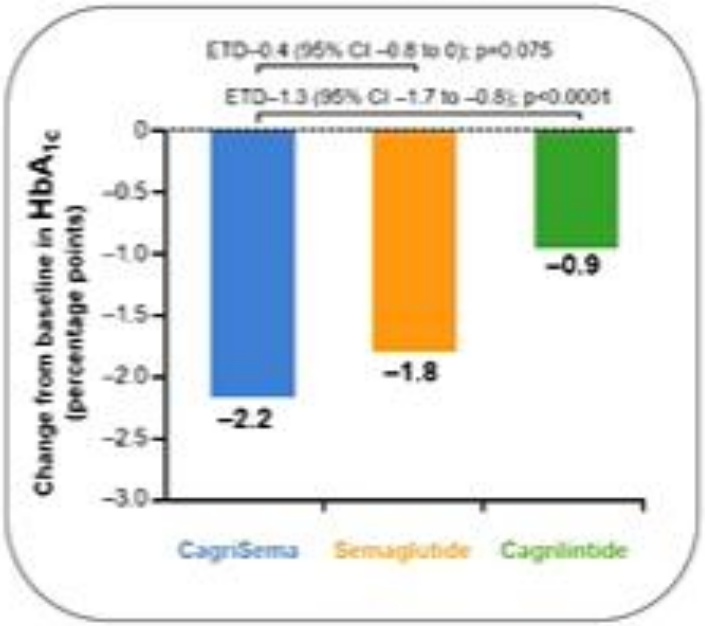
Efficacy and safety of co-administered once-weekly cagrilintide 2·4 mg with once-weekly semaglutide 2·4 mg in type 2 diabetes: a multicentre, randomised, double-blind, active-controlled, phase 2 trial

Body Weight Change

32 weeks



Change in HbA1c



N=92 / Age 58 yrs / BMI 35.5 / 36% Female / T2D - metformin (73%) +/- SGLT2i / baseline A1c 8.4%

Frias *et al*, Lancet, June, 2023

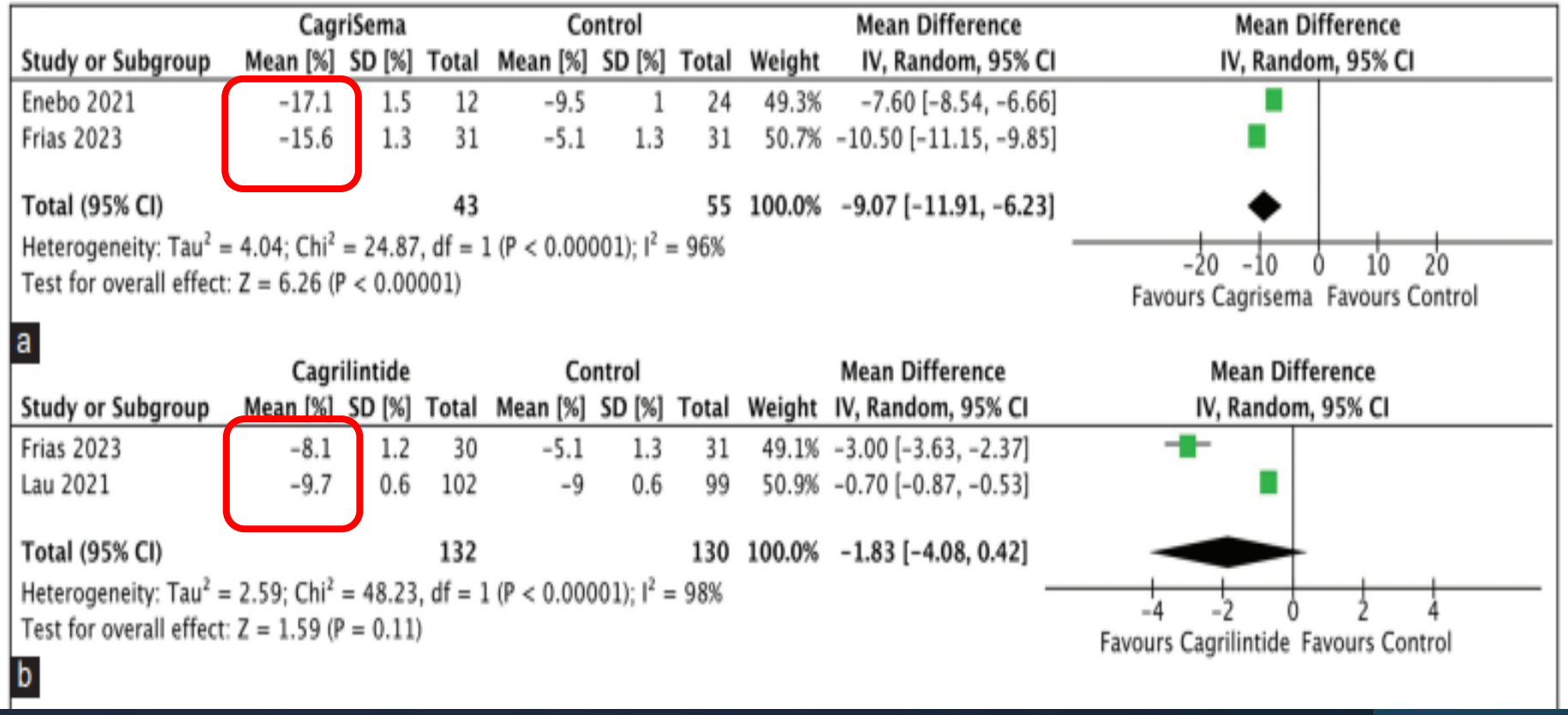
Yale SCHOOL OF MEDICINE

Systematic Review and Meta Analysis

Efficacy and Safety of Cagrilintide Alone and in Combination with Semaglutide (Cagrisema) as Anti-Obesity Medications: A Systematic Review and Meta-Analysis

Deep Dutta, Lakshmi Nagendra[1], H

Cagrisema supera a semaglutida en peso pérdida. Cagrilintida muestra una pérdida de peso comparable a la de semaglutida/liraglutida con vómitos significativamente menores



DUALES: GLP1R/GIPR

GLP1R/GIPR dual agonists in clinical development

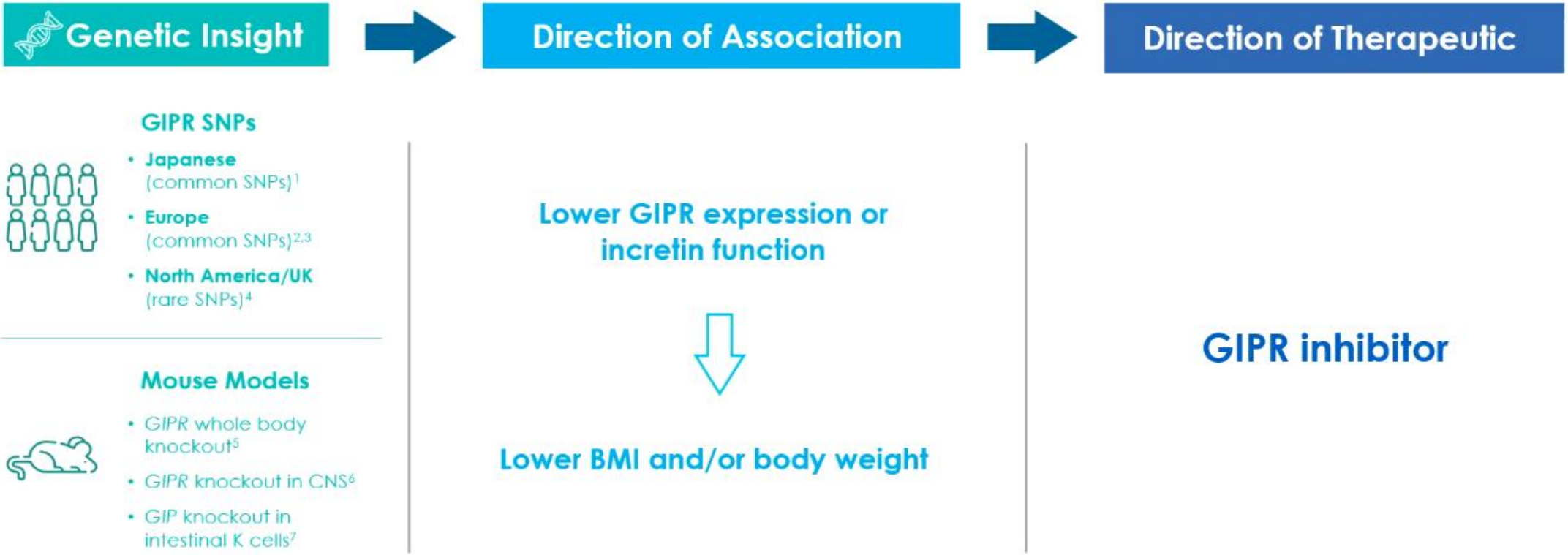
Name	Company	Class	Highest development phase	Current status of the ongoing trials/References
Tirzepatide (LY-3298176)	Eli Lilly and Company	Acylated long-acting GLP1R/ GIPR dual agonist	FDA/EMA approved (obesity) FDA/EMA approved (T2DM) Phase III (HF, SAS) Phase II (NASH)	• Substantial weight loss is achieved with a comparable safety profile to FDA-approved GLP1RAs. • It is FDA/EMA approved for T2DM based on SURPASS trials.[50–54] • It is FDA/EMA approved for chronic weight management based on the ongoing SURMOUNT trials.[55,56] • Currently, it is under investigation for NASH in the SYNERGY-NASH trial (NCT04166773).
Maridebart cafraglutide (AMG133)	Amgen	GLP1R agonist/ GIPR antagonist*	Phase II (obesity)	• Maridebart cafraglutide (AMG133) offers the advantage of a longer duration of action, requiring administration only once every four weeks (Q4W), reducing the frequency of treatment and potentially improving patient adherence. • Results of the phase I trial demonstrated substantial weight loss among the participants in the multiple ascending doses (MAD) cohort with a mean of−14.5% at its maximum dose (420 mg) compared to 1.49% in the placebo group by day 85 (NCT04478708).[57] • Currently, AMG133 is in phase II (NCT05669599).
CT388	Carmot Therapeutics	GLP1R/ GIPR modulator	Phase I/IIa (obesity)	• Double-blind RCT to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of CT-388 in otherwise healthy overweight and obese adult participants and in obese patients with T2DM (NCT04838405).

*Maridebart Cafraglutide (AMG133) is an antagonist at GIPR and an agonist at GLP1R, unlike Tirzepatide which is GLP1R/GIPR dual agonist.
EMA, European Medicines Agency; FDA, Food and Drug Administration; GIPR, glucose-dependent insulinotropic polypeptide receptor; GLP1R, glucagon-like peptide-1 receptor; GLP1RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; NASH, non-alcoholic steatohepatitis; RCT, randomized controlled trial; SAS, sleep apnoea syndrome; T2DM, type-2 diabetes mellitus

Maridebart Cafraglutide (MARITIDE) :

GIP antagonista y GLP-1agonista

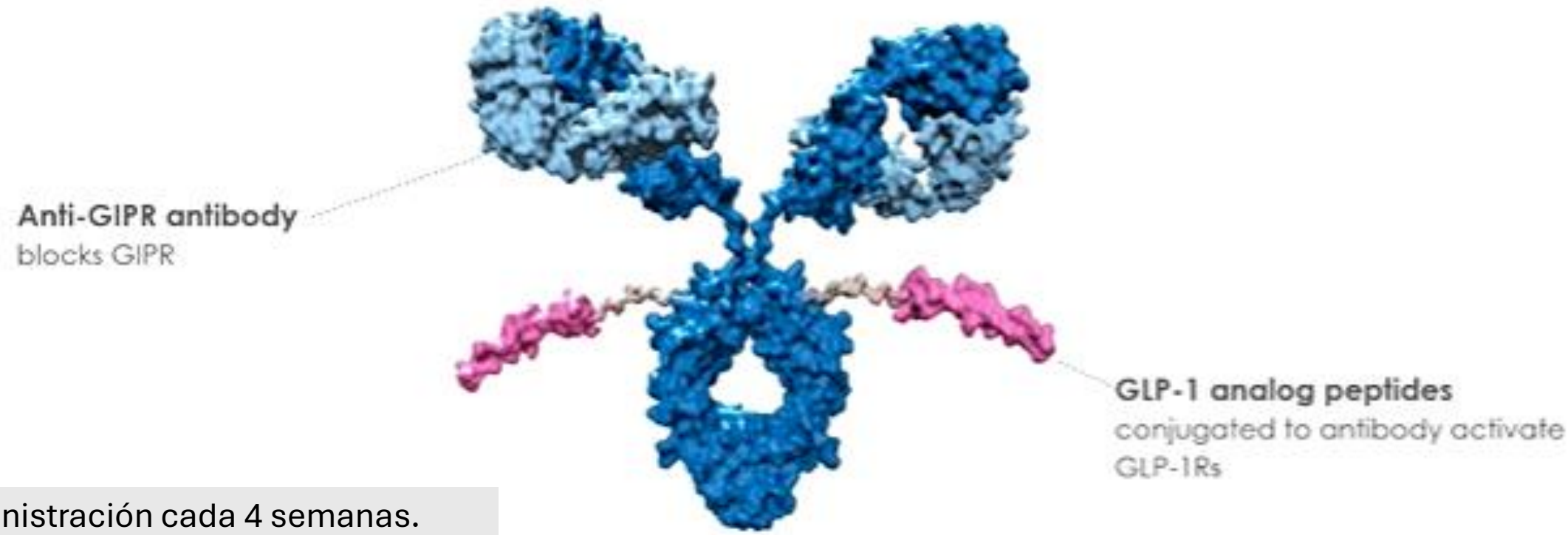
Human and mouse genetic studies support GIPR inhibition as the therapeutic direction for obesity



SNP, single nucleotide polymorphism

1. Okada Y, et al. *Nat Genet*. 2012;44:302-306. 2. Speliotes EK, et al. *Nat Genet*. 2010;42:937-948. 3. Berndt SI, et al. *Nat Genet*. 2013;45:501-512. 4. Akbari P, et al. *Science*. 2021;373:eabf8683. 5. Miyawaki K, et al. *Nat Med*. 2002;8:738-742. 6. Zhang Q, et al. *Cell Metab*. 2021;33:833-844. 7. Althage MC, et al. *J Biol Chem*. 2008;283:18365-18376.

Maridebart cafraglutide (MariTide) is a bispecific molecule: an anti-GIPR antibody conjugated to two GLP-1 analog peptides



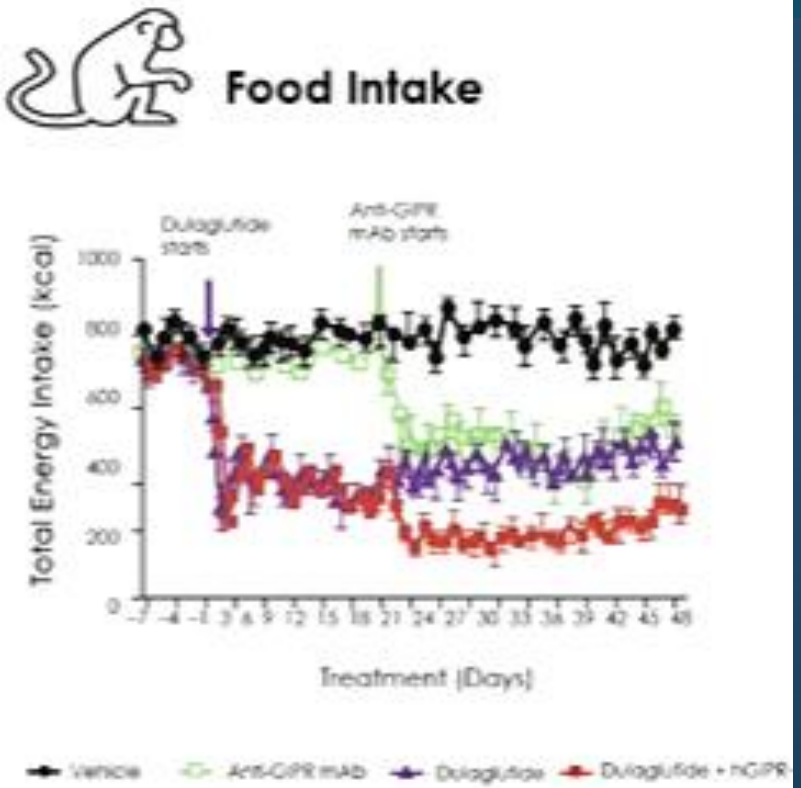
Administración cada 4 semanas.

Nat Metab. 2024 Feb;6(2):290-303. doi: 10.1038/s42255-023-00966-w.

Mouse anti-GIPR Ab synergizes with GLP-1 agonists to increase body weight loss in mice and nonhuman primates

Data in mice.
Similar data exist in nonhuman primates, not shown.

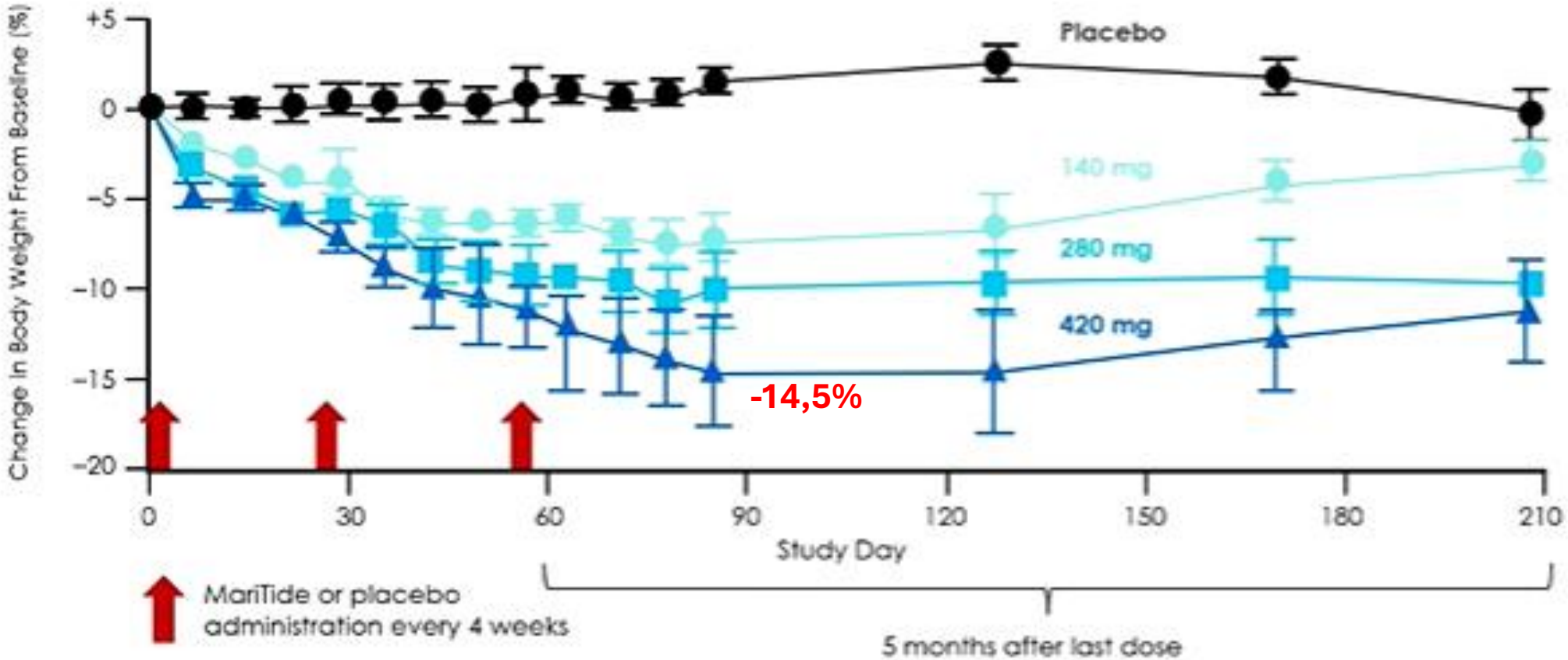
*P < 0.05 and ***P < 0.001 vs vehicle.
Ab, antibody; mAb, monoclonal antibody.
Killion EA, et al. Sci Transl Med. 2018;10:eaat3092.



AMGEN

Nat Metab. 2024 Feb;6(2):290-303. doi: 10.1038/s42255-023-00966-w.

MariTide phase 1 results: weight reduction was maintained following the last dose



Nat Metab. 2024 Feb;6(2):290-303. doi: 10.1038/s42255-023-00966-w.

TRIPLE AGONISTAS GLP1R/GCGR/GIPR

Table 5: GLP1R/GCGR/GIPR triple agonists in clinical development

Name	Company	Class	Highest development phase	Current status of the ongoing trials/References
Retatrutide (LY3437943)	Eli Lilly and Company	GLP1R/ GCGR/GIPR tri-agonist	Phase III (obesity/ CVD) Phase II (T2DM)	• Retatrutide (LY3437943), favouring GIPR but with balanced GLP1R and GCGR activity, demonstrates a safety profile similar to GLP1R mono-agonists. The GLP1R/GCGR/GIPR balance of LY3437943 is 1:1:10. It exhibits a similar safety profile to GLP1R mono-agonists, with mild tachycardia.[79] • In a phase I trial involving healthy individuals, administration of a single dose of LY3437943 was well tolerated and resulted in significant weight reduction, which was sustained for up to 43 days.[79] The results were comparable to four weeks of Tirzepatide injections.[3] The satisfactory safety, tolerability, and efficacy observed in this study support further investigation of LY3437943 using multiple doses in IWO and T2DM • A phase Ib trial involving individuals with T2DM confirmed a significant decrease in blood glucose and weight over 12 weeks of treatment while maintaining tolerability and safety.[80] • The latest findings from a Phase II trial (NCT04881760) revealed that after 48 weeks, the groups receiving 1 mg, 4 mg, 8 mg, and 12 mg doses experienced a decrease in body weight by −8.7%, −17.1%, −22.8%, and −24.2%, respectively, as compared to −2.1% in the placebo group (estimated treatment difference, Retatrutide 12 mg vs Placebo of −22.1%; 95% CI: −24.9% to −19.3%). Additionally, 60% of the participants achieved a weight reduction of 15% or above. In terms of safety, the most common AEs observed were gastrointestinal in nature, indicating that Retatrutide's safety profile is comparable to other incretin-based therapies.[81] Results of phase II were presented in ADA 2023. The historic debut of Retatrutide stole headlines, with weight loss rivalling that of bariatric and metabolic surgery, with weight loss reaching up to 24.2%.[82] • In May 2023, Eli Lilly and Company initiated • a phase III trial (TRIUMPH-3; NCT05882045) to investigate the effects of Retatrutide on individuals with severe obesity and existing CVD. This trial is expected to conclude in November 2025.
SAR 441255	Sanofi	GLP1R/ GCGR/GIPR tri-agonist	Phase I (obesity; T2DM)	• SAR441255 is a synthetic peptide triagonist developed to target multiple receptors, including GLP1R, GCGR, and GIPR. This triagonist is structurally based on the exendin-4 sequence and has shown potential in various studies for improving weight loss and glycaemic control in individuals, particularly in those with obesity and diabetes.[82] • SAR441255 has demonstrated the ability to ameliorate body weight in obese individuals, including diabetic cynomolgus monkeys.[82] • In October 2019, Sanofi reported discontinuation of SAR 441255 development in type 2 diabetes mellitus and obesity
Efocipegtrutide (HM15211)	Hanmi Pharmaceutical	GLP1R/ GCGR/GIPR tri-agonist	Phase II (NASH)	• HM15211, a third GLP1R/GCGR/GIPR tri-agonist peptide, effectively reduces hepatic lipid and body weight in IWO and NAFLD. It is being evaluated in phase II trials (NCT04505436) to treat NASH.[83]

ADA, American Diabetes Association; AEs, adverse events; CVD, cardiovascular disease; GCGR, glucagon receptor; GIPR, glucose-dependent insulinotropic polypeptide receptor; GLP1R, glucagon-like peptide-1 receptor; GLP1RA, glucagon-like peptide-1 receptor agonist; IWO, individuals with obesity; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; T2DM, type-2 diabetes mellitus

etatrutide: Resultados-Fase 2

Diabetes tipo 2

Articles

www.thelancet.com **Published online June 26, 2023 https://doi.org/10.1016/S0140-6736(23)01053-X**

Retatrutide, a GIP, GLP-1 and glucagon receptor agonist, for people with type 2 diabetes: a randomised, double-blind, placebo and active-controlled, parallel-group, phase 2 trial conducted in the USA

Julio Rosenstock, Juan Frias, Ania M Jastreboff, Yu Du, Jitong Lou, Sirel Gurbuz, Melissa K Thomas, Mark L Hartman, Axel Haupt, Zvonko Milicevic, Tamer Coskun

Obesidad

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Triple–Hormone-Receptor Agonist Retatrutide for Obesity — A Phase 2 Trial

Ania M. Jastreboff, M.D., Ph.D., Lee M. Kaplan, M.D., Ph.D., Juan P. Frías, M.D., Qiwei Wu, Ph.D., Yu Du, Ph.D., Sirel Gurbuz, M.D., Tamer Coskun, M.D., Ph.D., Axel Haupt, M.D., Ph.D., Zvonko Milicevic, M.D., and Mark L. Hartman, M.D., for the Retatrutide Phase 2 Obesity Trial Investigators*

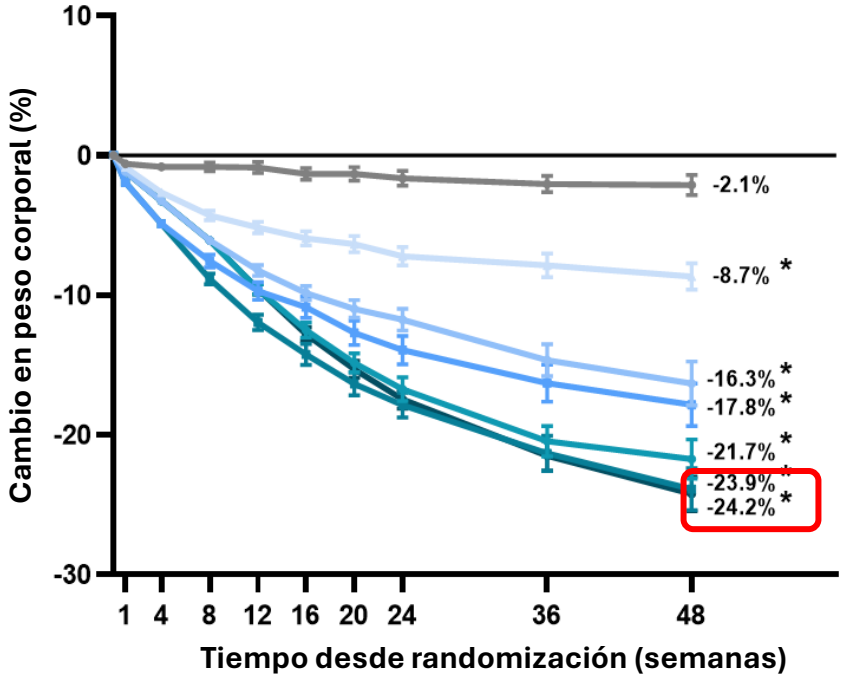
N Engl J Med. 2023 Aug 10;389(6):514-526

Reducción de peso corporal en el tiempo

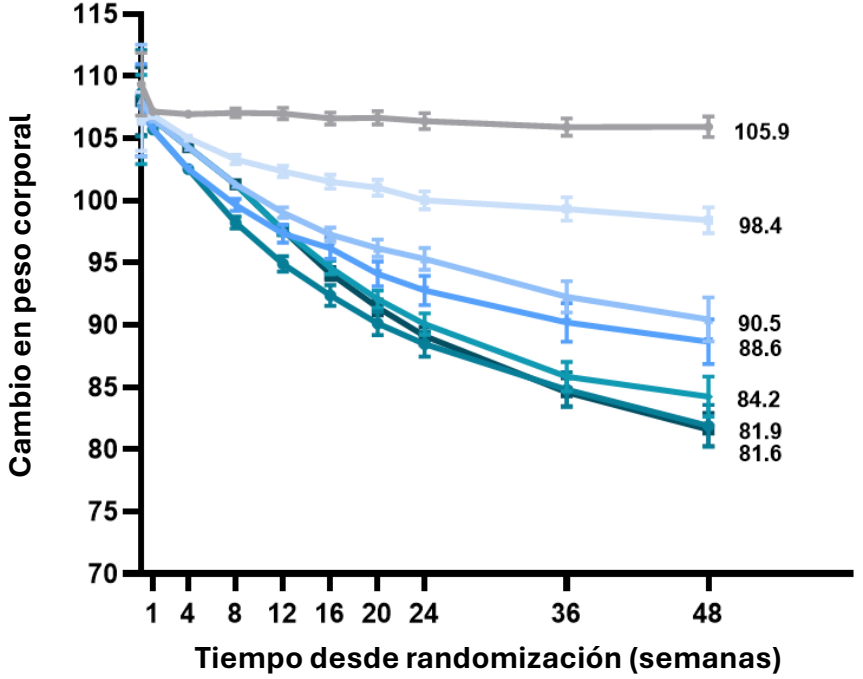
Ensayo clínico fase 2 de Retatrutida en participantes con obesidad sin DM2

Obesidad

% de cambio en peso corporal a semana 48 respecto al inicio



Cambio en peso corporal a semana 48 respecto al inicio



Placebo | Reta 1 mg | Reta 4 mg (DI 2 mg) | Reta 4 mg (DI 4 mg) | Reta 8 mg (DI 2 mg) | Reta 8 mg (DI 4 mg) | Reta 12 mg (DI 2 mg)

A la semana 48 el % de cambio en los grupos RETA fue **−8.7% to −24.2**% vs −2.1% con PBO

Nota: Datos indican MMC (EE); Barras de error indican EE. **P*<.001 vs. placebo. DI=Dosis inicial; MMC=Media de mínimos cuadrados; Reta=Retatrutida; EE= Error estándar; DM2=Diabetes tipo 2. **P*<.001 vs. placebo.

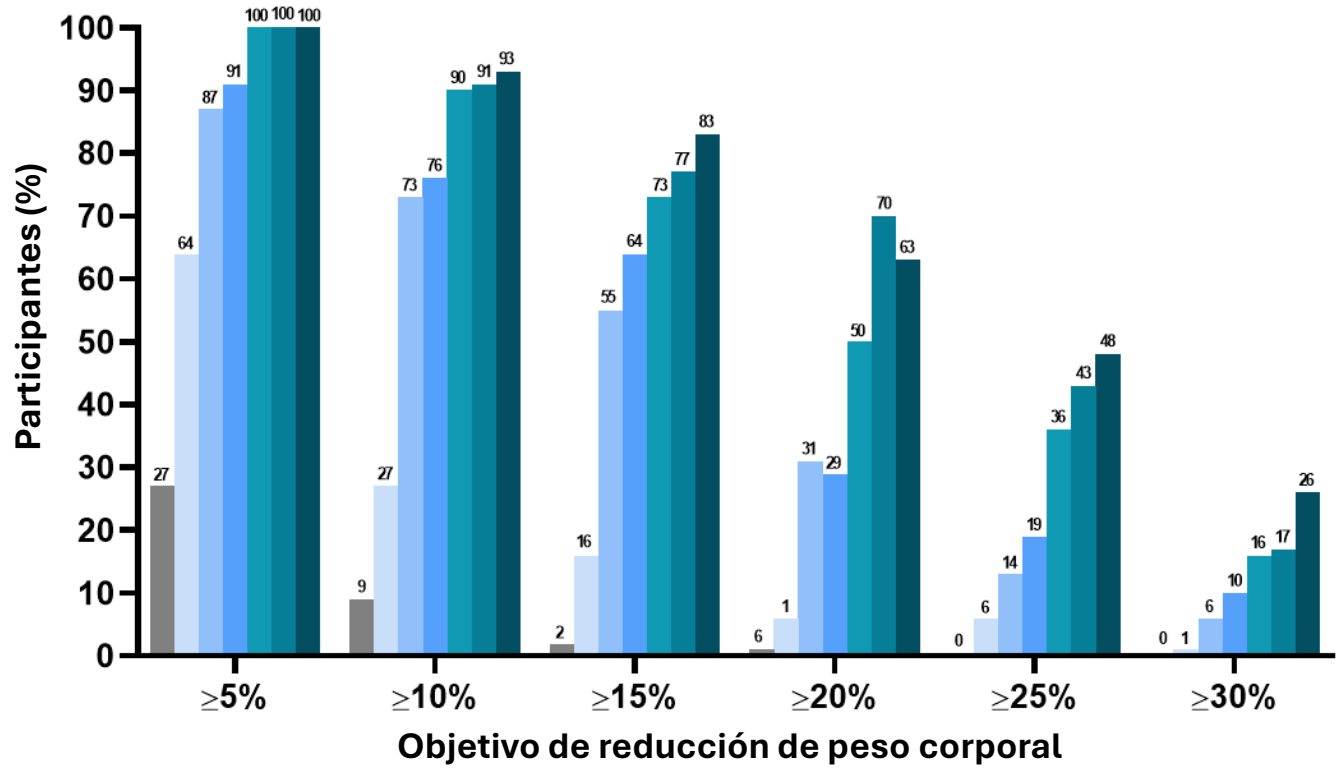
Jastreboff AM, et al. *NEMJ.* 2023;.

Proporción de participantes que alcanzan objetivos de reducción de peso corporal

Ensayo clínico fase 2 de Retatrutida en participantes con obesidad sin DM2

Obesidad

Participantes que alcanzan objetivos de reducción de peso corporal a la semana 48

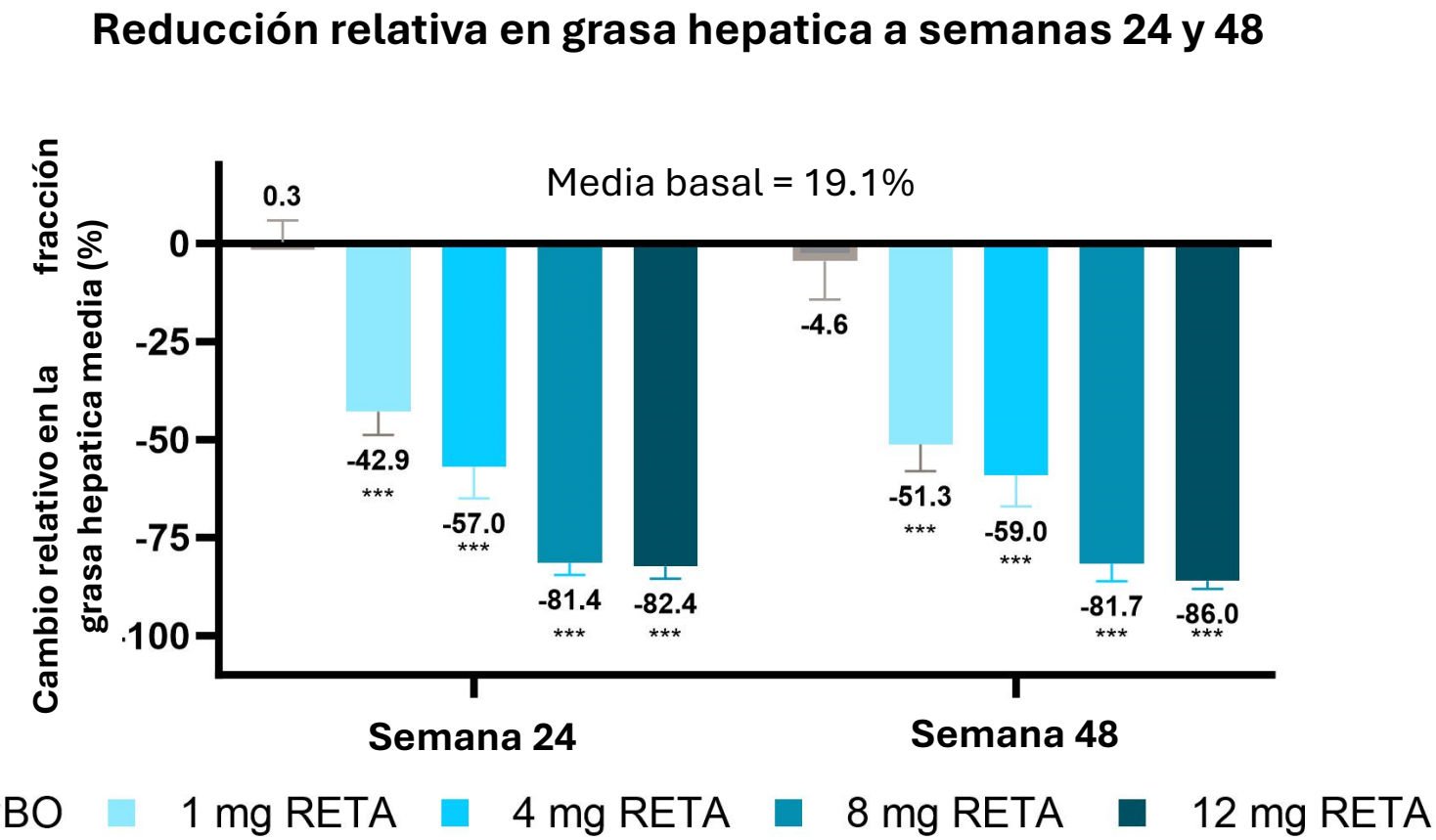


DI=Dosis inicial; Reta=Retatrutida; DM2= Diabetes tipo 2.
Jastreboff AM, et al. *NEMJ*. 2023;(Aceptado).

- **100% de los participantes con RETA 8 mg and 12 mg alcanzan una reducción de peso de >5%**
- Reducciones de ≥10% y ≥15% se alcanzaron en más participantes con RETA (todas las dosis) vs PBO
- Más participantes con RETA≥4 mg alcanzaron reducciones de peso de ≥20% y ≥25% vs PBO
- **26% de los participantes de RETA 12mg alcanzaron ≥30% de reducción de peso corporal**

Retatrutida en Obesidad sin DM2 : subestudio MASLD

- El cambio relativo en grasa hepática fue mayor en todas las dosis de RETA vs. PBO
- La reducción relativa en grasa hepática fue de >80% con RETA 8 mg y 12 mg



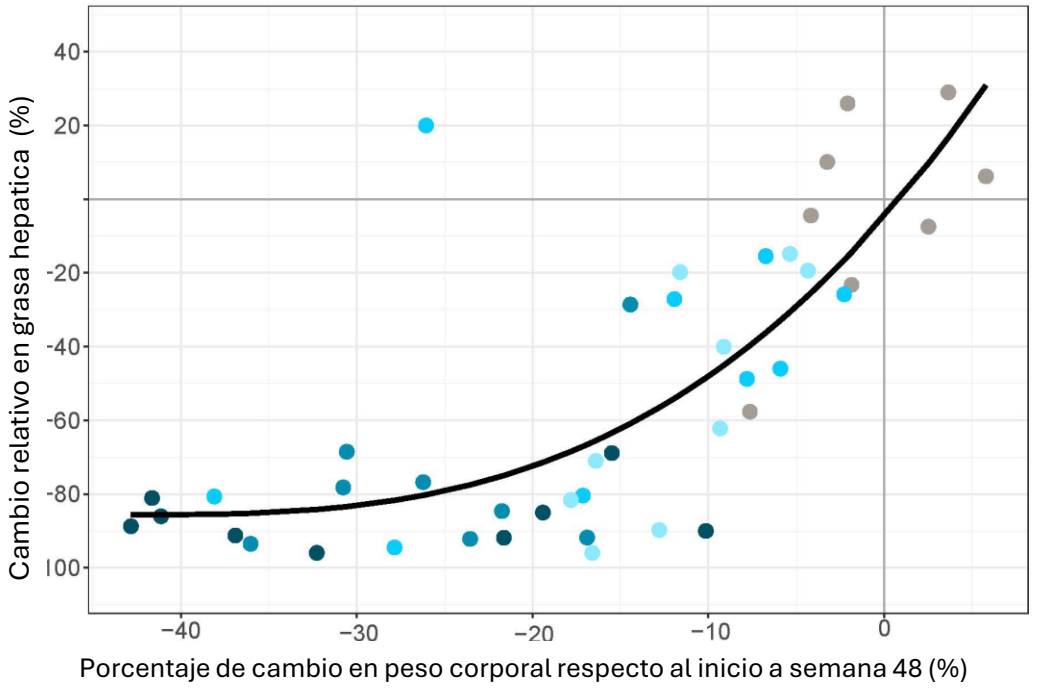
***p<0.001 vs. PBO.

[a]Pocos participantes se realizaron RMN a la semana 48 (n=8 [PBO], n=9 [1 mg RETA], n=9 [4 mg RETA], n=8 [8 mg RETA], n=9 [12 mg RETA]) comparado con la semana 24 (n=14 [PBO], n=16 [1 mg RETA], n=15 [4 mg RETA],n=17 [8 mg RETA], n=15 [12 mg RETA]). RMN=Resonancia magnética nuclear; PBO=placebo; RETA=retatrutida.

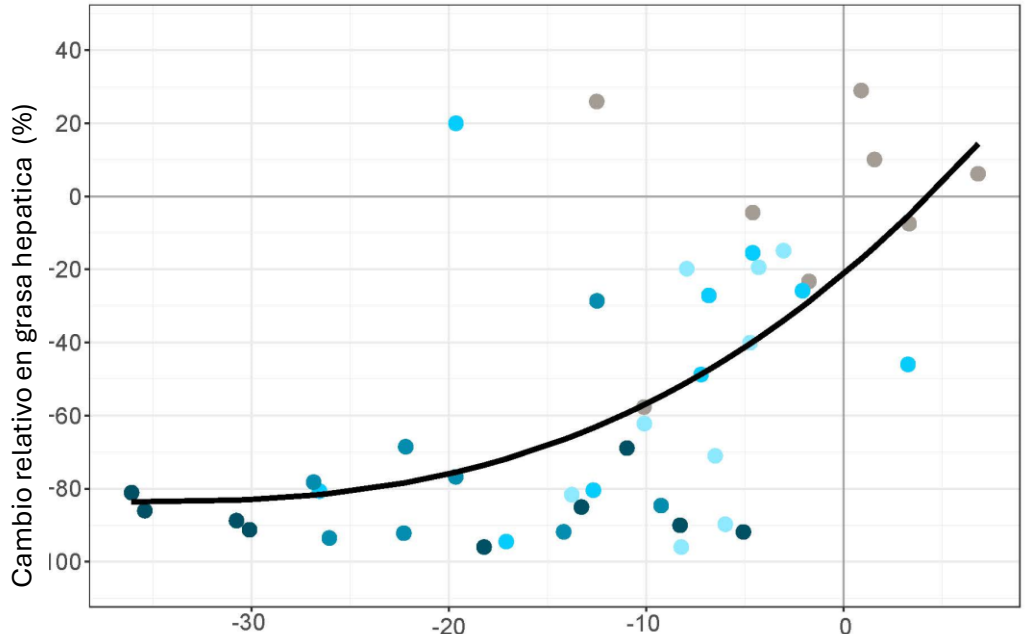
1. Arun J Sanyal et al American Association for the Study of Liver Disease (AASLD) – The Liver Meeting; Boston, MA, USA; 10 - 14 November 2023- abstract, #148

Correlaciones con cambio en grasa hepática: Peso corporal y perímetro de cintura a la semana 48

Peso corporal



Perímetro de cintura



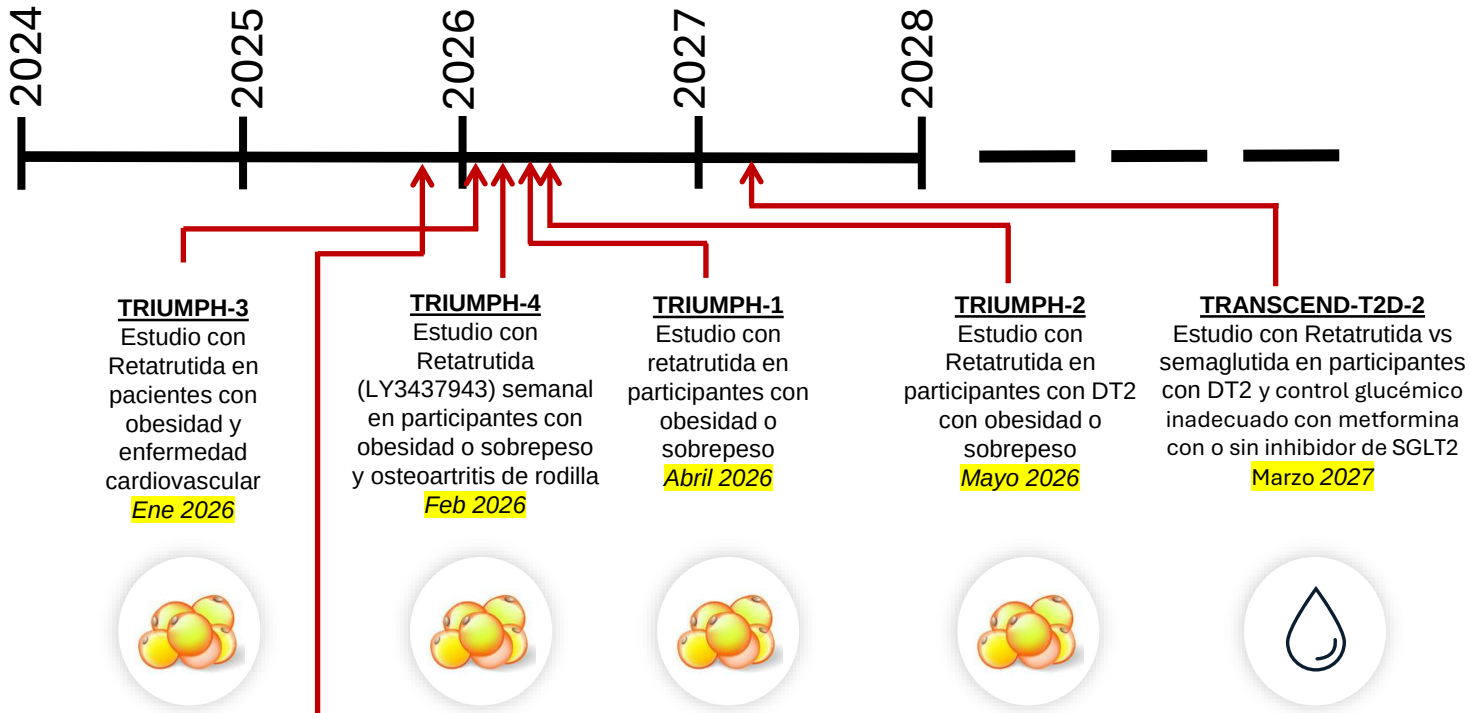
PBO 1 mg RETA 4 mg RETA 8 mg RETA 12 mg RETA

Las reducciones en grasa hepatica más elevadas se alcanzaron con un ~20% de reducción de peso corporal

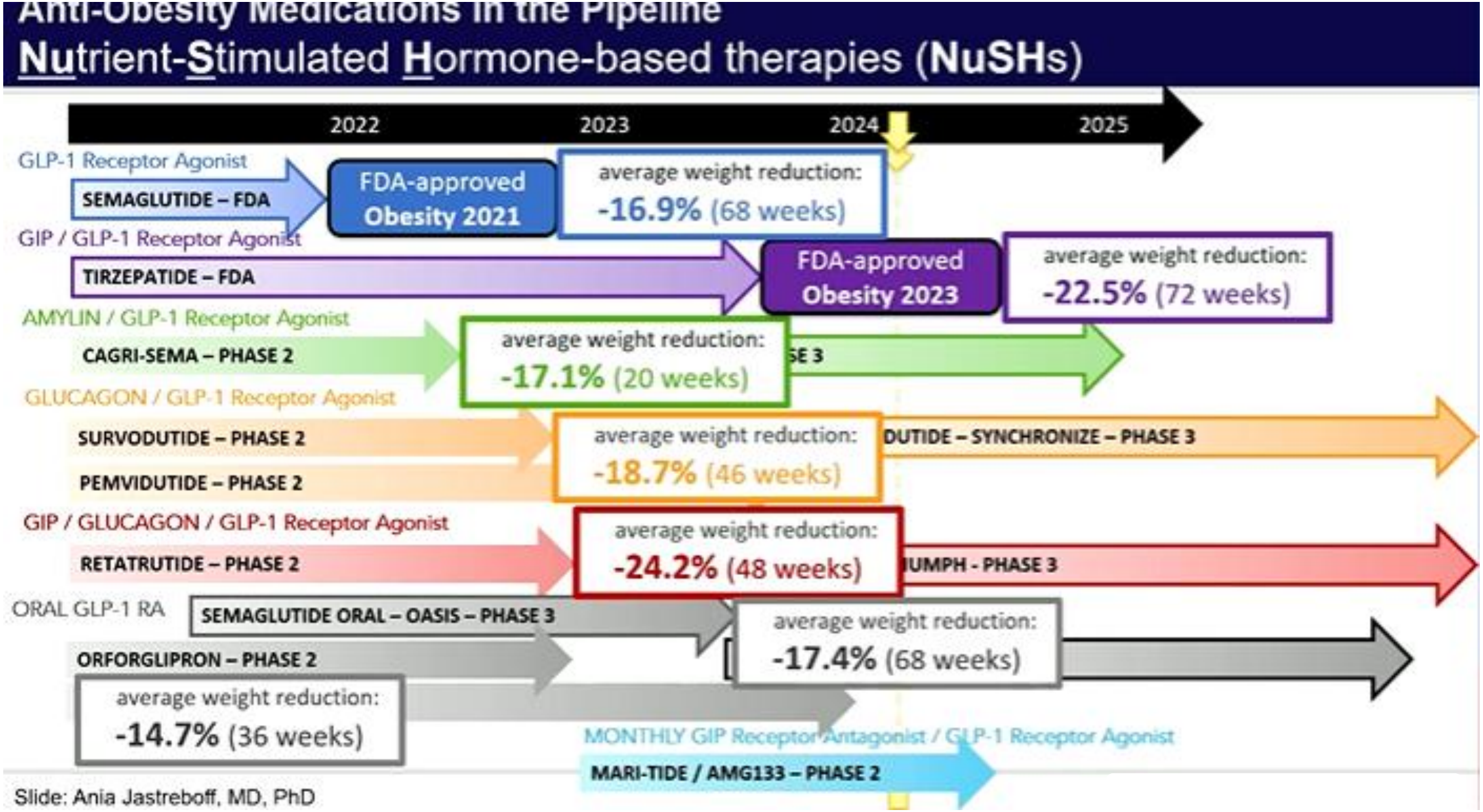
Diagrama de dispersión y curvas de modelo de potencia ajustadas

1. Arun J Sanyal et al American Association for the Study of Liver Disease (AASLD) – The Liver Meeting; Boston, MA, USA; 10 - 14 November 2023- abstract, #148

Programa clínico de Fase 3 con Retatrutida



TRIUMPH-1:NCT05929066
TRIUMPH-2: NCT05929079
TRIUMPH-3: NCT05882045
TRIUMPH-4: NCT05931367
TRANSCEND-T2D-2: NCT06260722
F2b-Funcion renal: NCT05936151


Anti-Obesity Medications in the Pipeline
Nutrient-Stimulated Hormone-based therapies (NuSHs)
2022
2023
2024
2025
GLP-1 Receptor Agonist
SEMAGLUTIDE – FDA
FDA-approved Obesity 2021
average weight reduction: -16.9% (68 weeks)
GIP / GLP-1 Receptor Agonist
TIRZEPATIDE – FDA
FDA-approved Obesity 2023
average weight reduction: -22.5% (72 weeks)
AMYLIN / GLP-1 Receptor Agonist
CAGRI-SEMA – PHASE 2
average weight reduction: -17.1% (20 weeks)
GLUCAGON / GLP-1 Receptor Agonist
SURVODUTIDE – PHASE 2
PEMVIDUTIDE – PHASE 2
average weight reduction: -18.7% (46 weeks)
GIP / GLUCAGON / GLP-1 Receptor Agonist
RETATRUTIDE – PHASE 2
average weight reduction: -24.2% (48 weeks)
ORAL GLP-1 RA
SEMAGLUTIDE ORAL – OASIS – PHASE 3
ORFORGLIPRON – PHASE 2
average weight reduction: -17.4% (68 weeks)
average weight reduction: -14.7% (36 weeks)
MONTHLY GIP Receptor Antagonist / GLP-1 Receptor Agonist
MARI-TIDE / AMG133 – PHASE 2
Slide: Ania Jastreboff, MD, PhD