Congresso congiunto
AMD - SID Piemonte - V. d'Aosta.

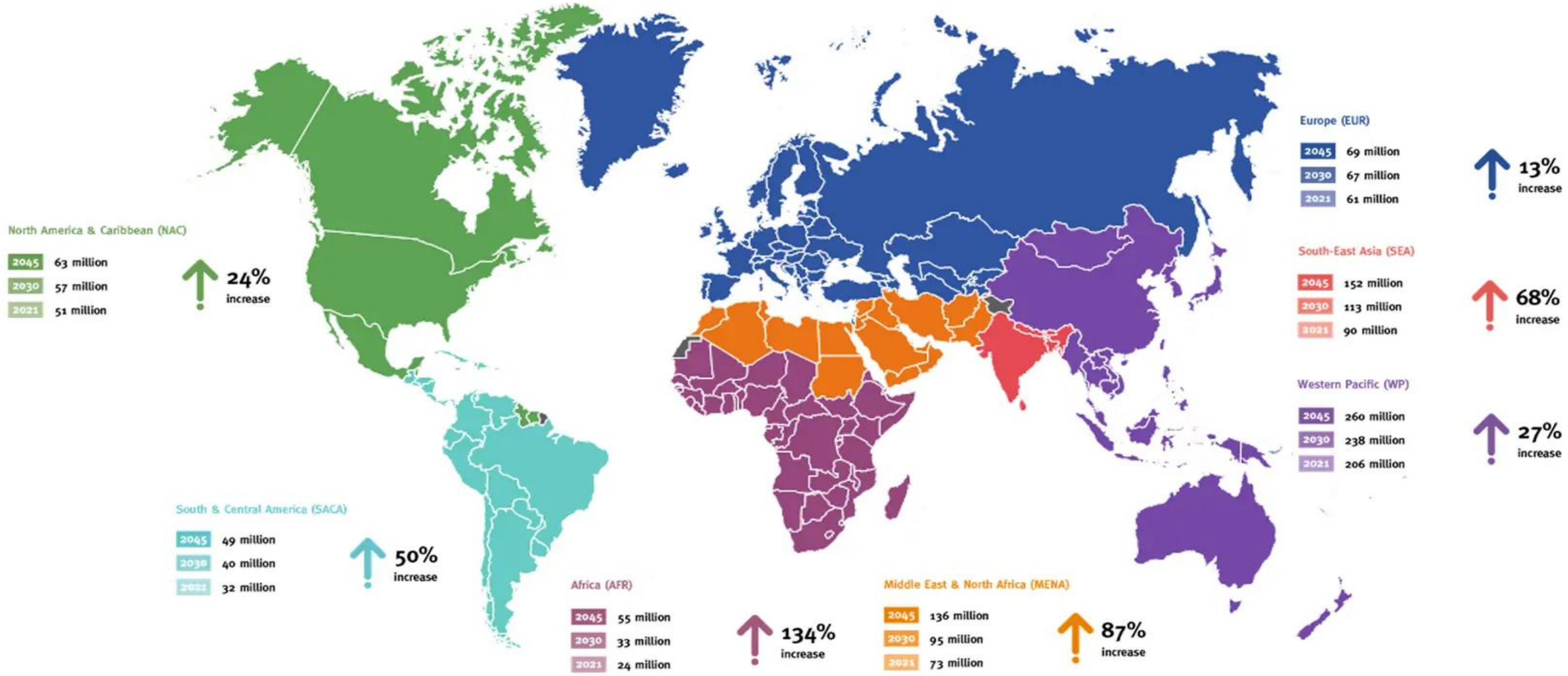
"Happy Birthday:"
Forever young
Innovazione farmacologica e tecnologica:
Il futuro della Diabetologia

Centro Congressi
The Place TORINO
11-12 ottobre
2024

Il futuro del Diabete mellito tipo 2

Dott.ssa Valeria Cambria
SSD Endocrinologia e Diabetologia
ASL VC

Il futuro… dell'epidemiologia

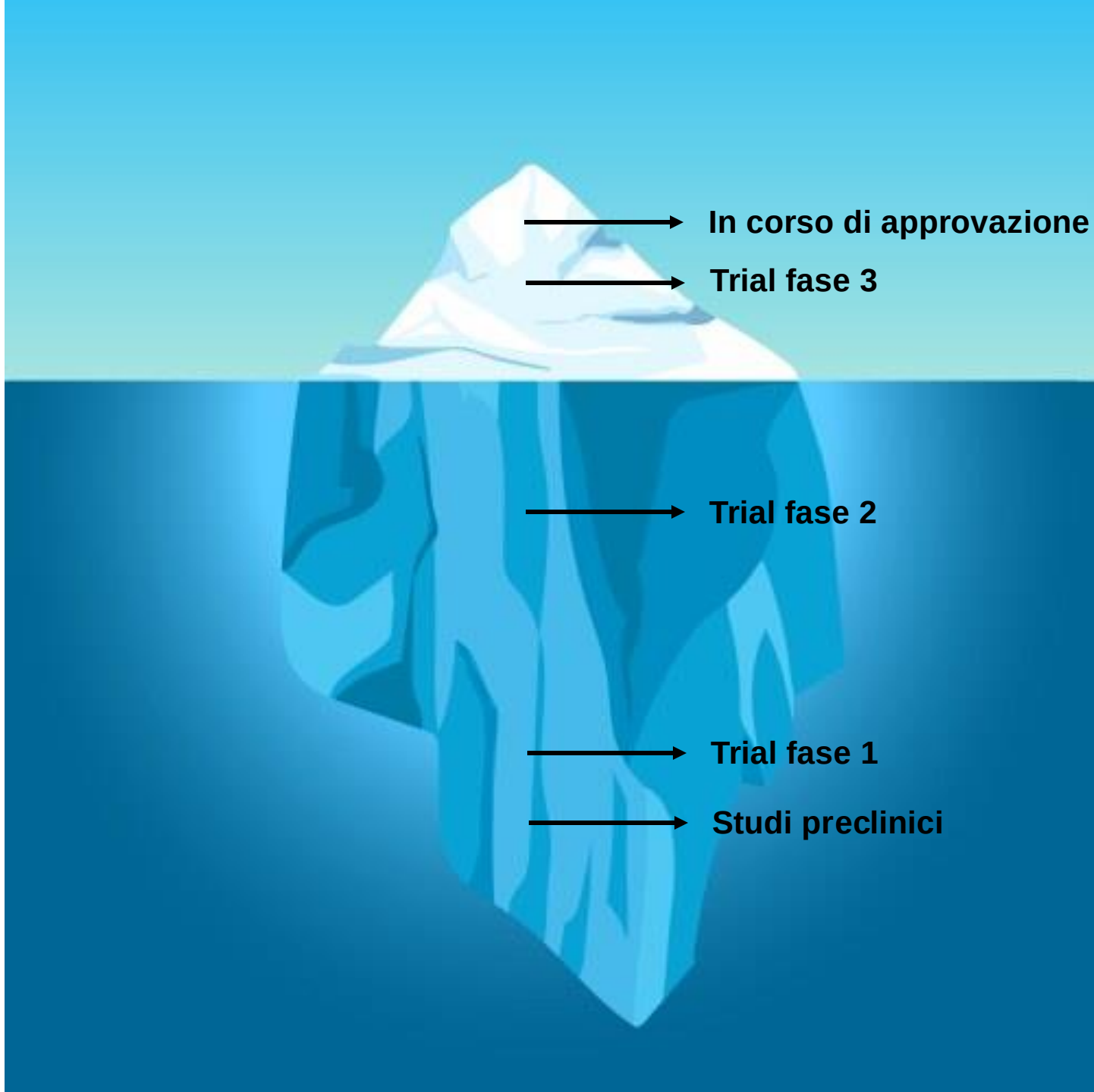


IDF Diabetes Atlas, 10th Edition, 2021

Disease-modifying drugs?

Agenda

- Futuro a breve termine
- Futuro a medio termine
- Futuro a lungo termine
- Futuro delle complicanze



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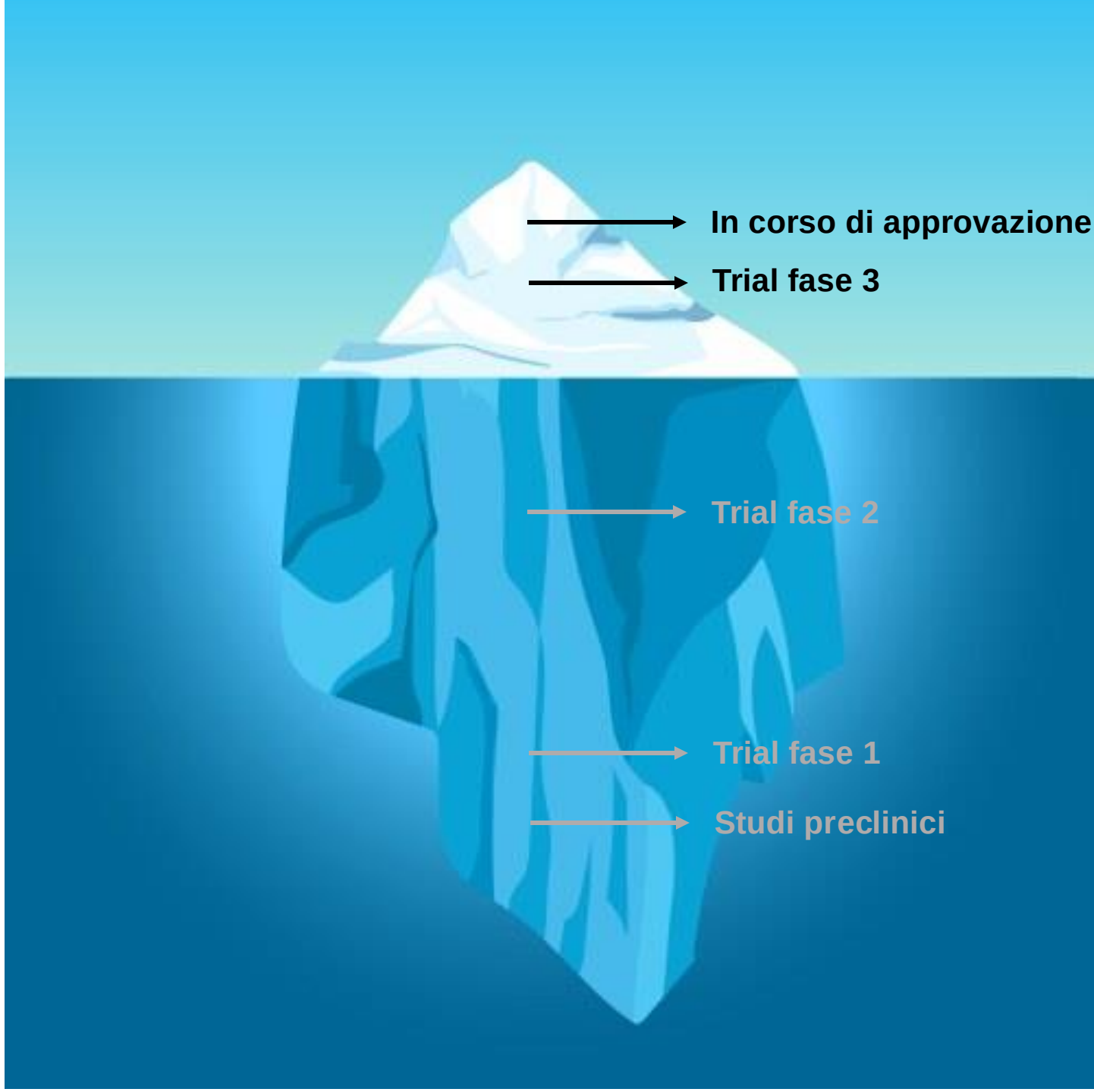


AID nel diabete di tipo 2

SECURE-T2D pivotal trial

305 pazienti con DM2
Terapia basal-bolus, premix, basal-only
HbA1c < 12%

2 settimane
Terapia Standard (ST)

13 settimane AID

Medscape Medical News > FDA Approvals

FDA Clears the Omnipod 5 System for Type 2 Diabetes

Miriam E. Tucker
August 26, 2024

HbA1c media baseline vs fine studio:
8.2 ± 1.3% vs 7.4 ± 0.9% (P<0.001)
-0.8% (CI 95%: -1.0, -0.7)

Nei pazienti con HbA1c >9%
HbA1c media ST vs 13 sett AID:
10.1% vs 8.1% (CI 95%: -2.3, -1.9)

TIR (70-180 mg/dl) medio ST vs AID:
45% vs 66% (p<0.001)
+ 4.8 hours/day

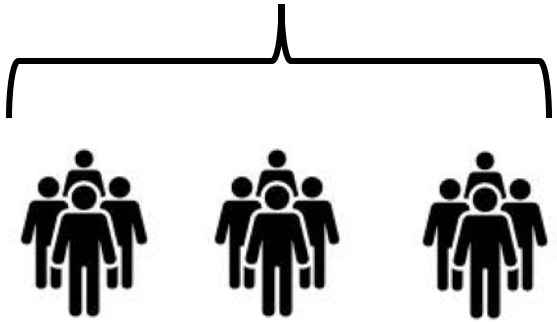
Pasquel FJ et al. Presented at: ADA, June 21-24, 2024; Orlando, FL

Semaglutide orale ad alti dosaggi

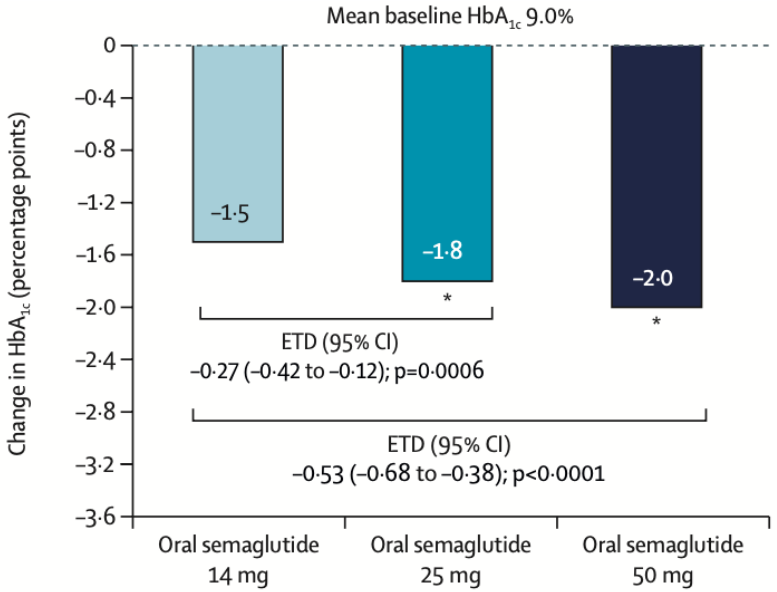
PIONEER PLUS

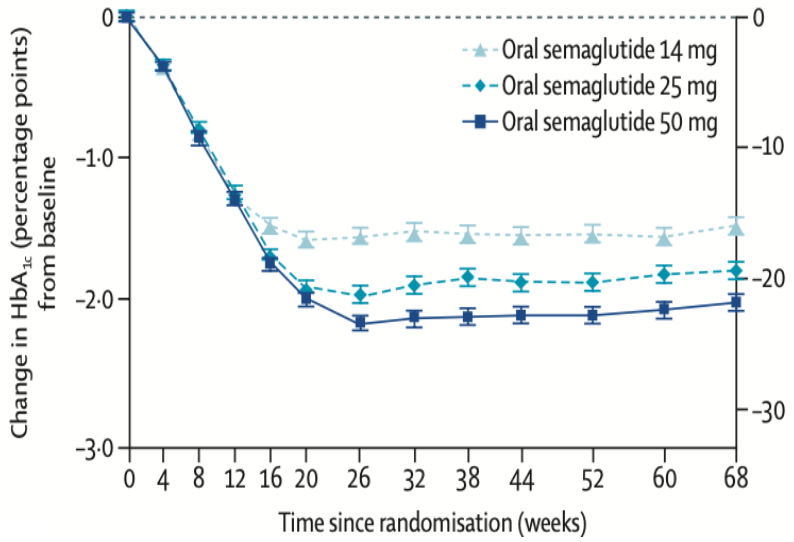
Trial fase 3b

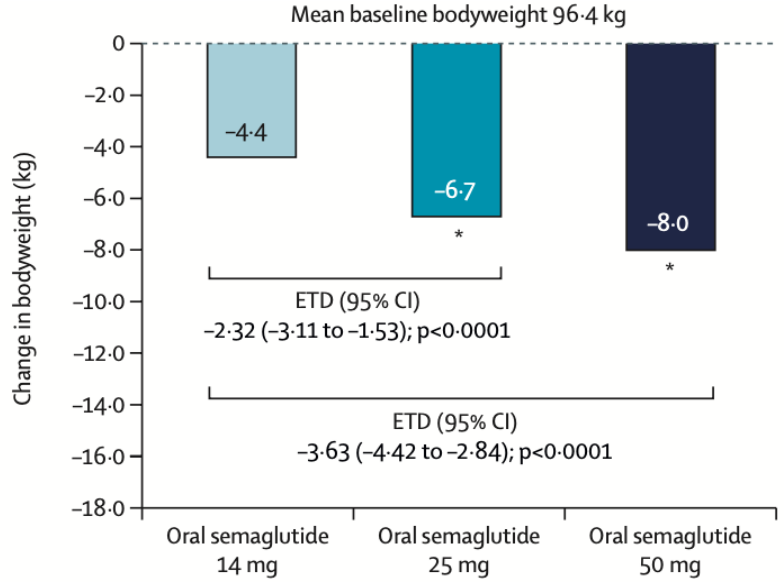
1606 pazienti
HbA1c media 9.0 ± 0.8%
BMI medio 33.8 ± 6.3 kg/m²

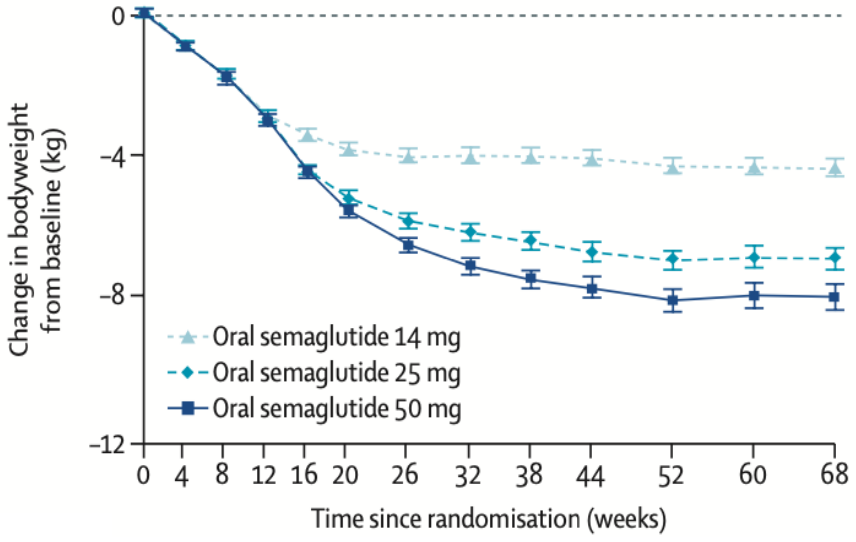


14 mg 25 mg 50 mg









Aroda VR et al, Lancet 2023; 402: 693-704

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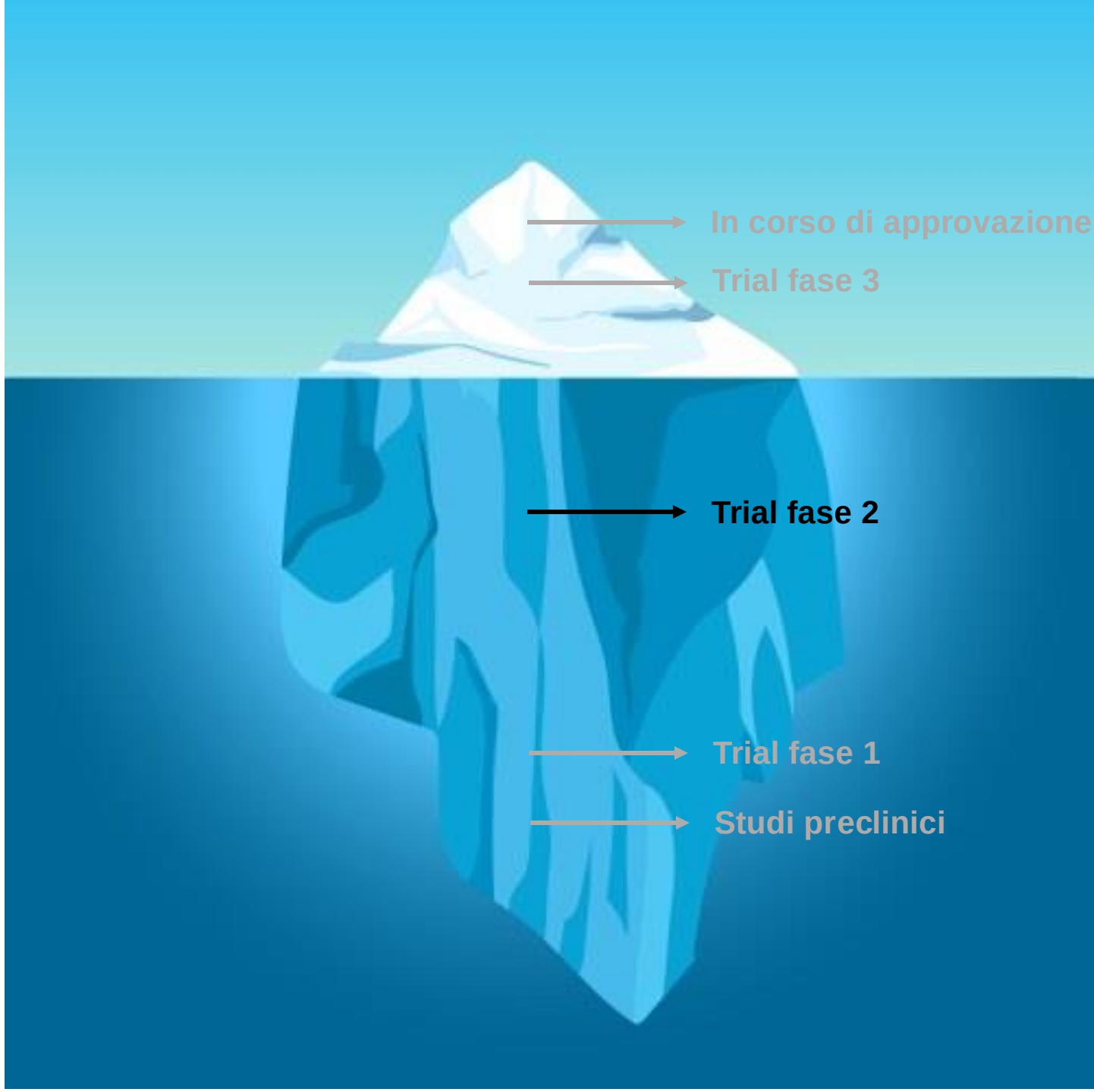
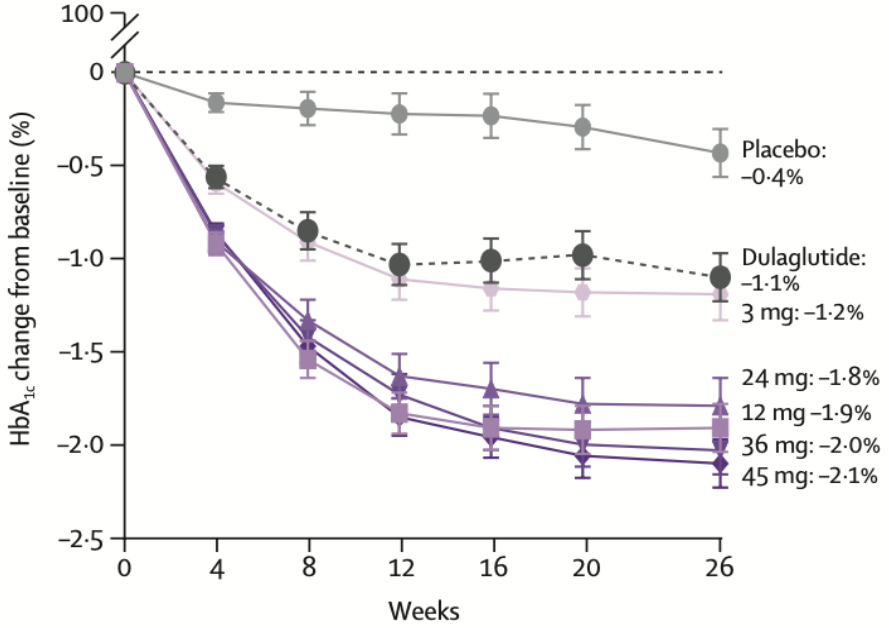
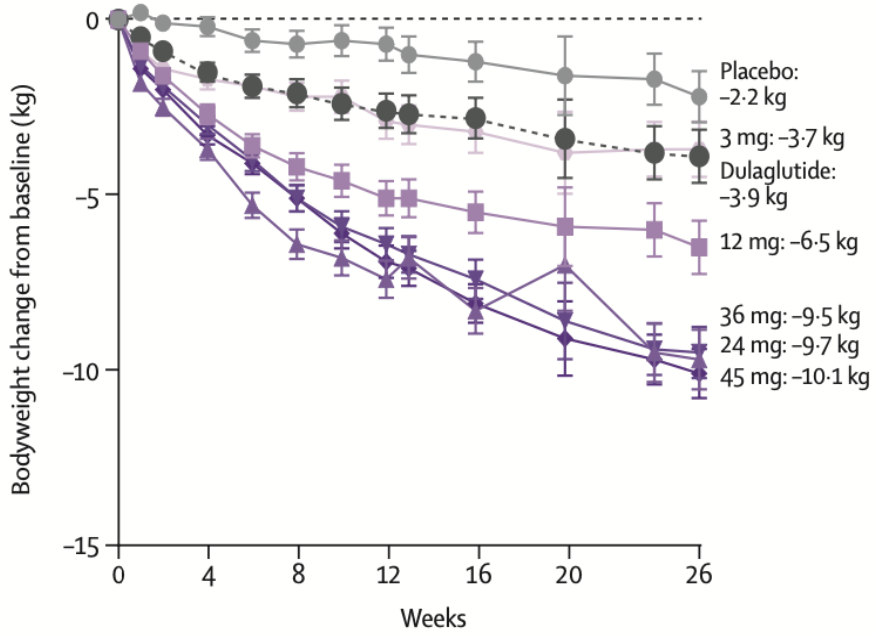


Orforglipron

GLP-1 RA non peptidico
NCT05048719
Trial fase 2

383 pazienti
HbA1c media 8.1 ± 0.9%
BMI medio 35.2 ± 6.2 kg/m^2





Frias JP et al, Lancet 2023; 402: 472-483

Danuglipron

NCT04617275
Trial fase 2a

123 pazienti con DM2, 28 con obesità
HbA1c media 8.19 ± 1.04%
BMI medio 37.3 ± 4.08 kg/m^2

Placebo

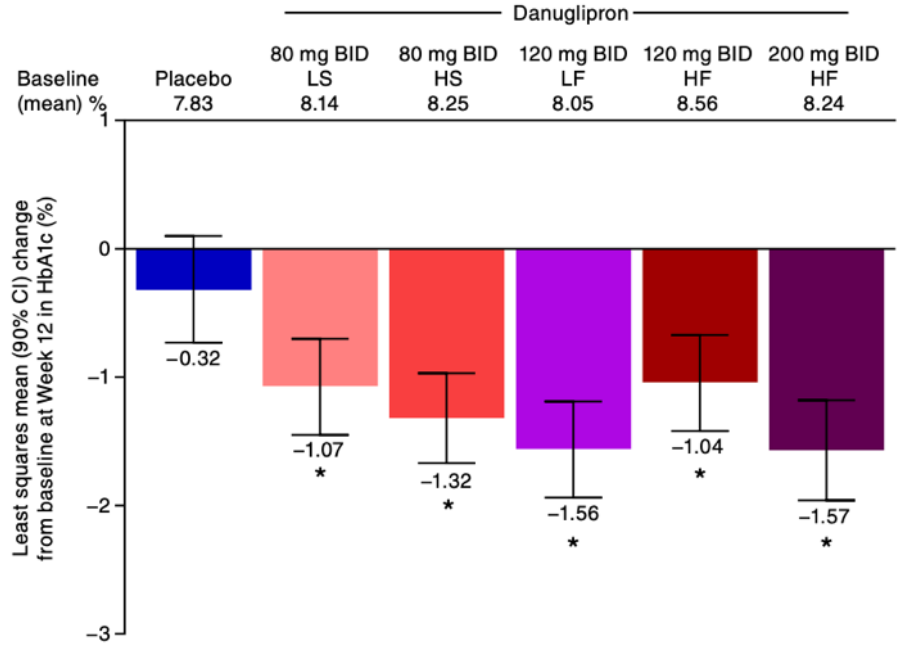
Danuglipron
80 mg BID LS

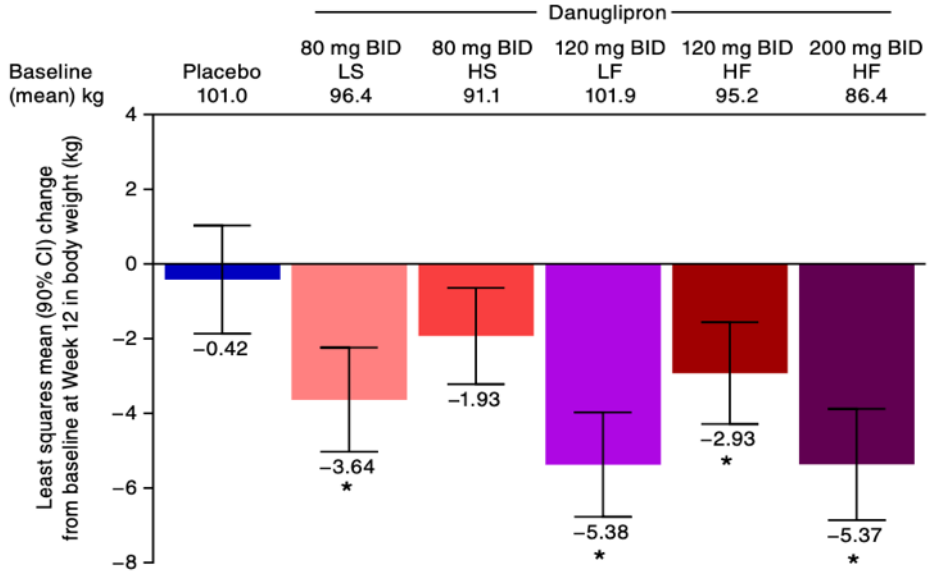
Danuglipron
80 mg BID HS

Danuglipron
120 mg BID LF

Danuglipron
120 mg BID HF

Danuglipron
200 mg BID HF



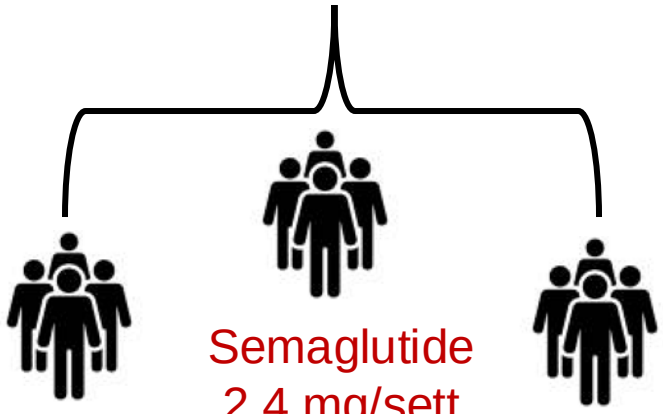


Saxena AR et al, Diabetes Obes Metab 2023; 25: 2805-2814

CagriSema

NCT04982575
Trial fase 2

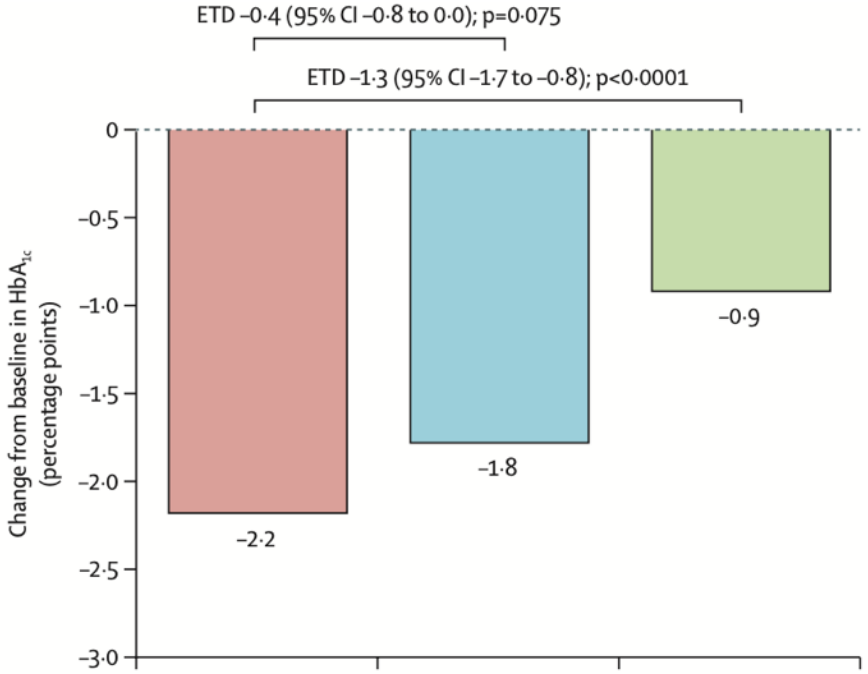
92 pazienti
HbA1c media 8.4 ± 0.8%
BMI medio 35.9 ± 5.7 kg/m^2

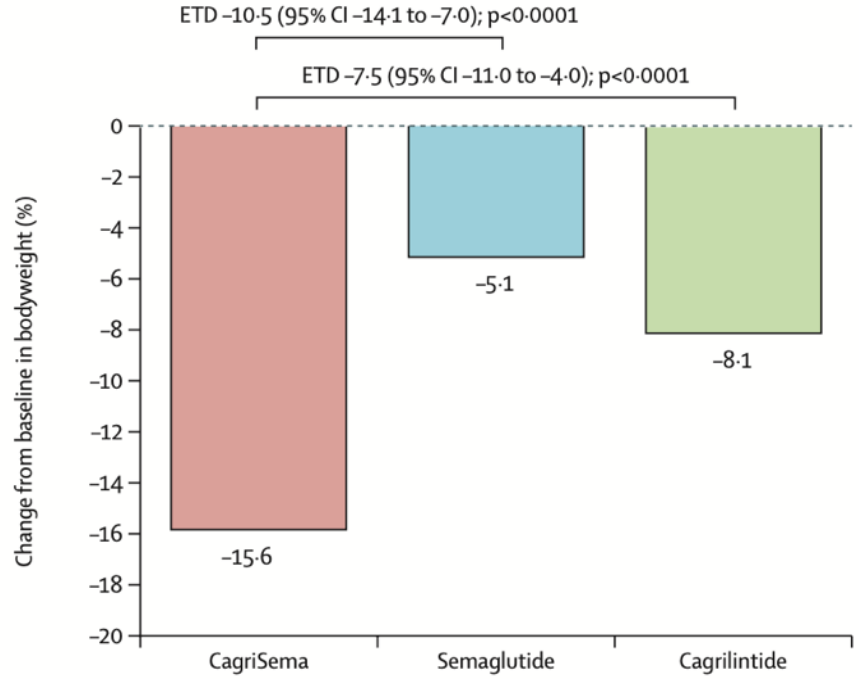


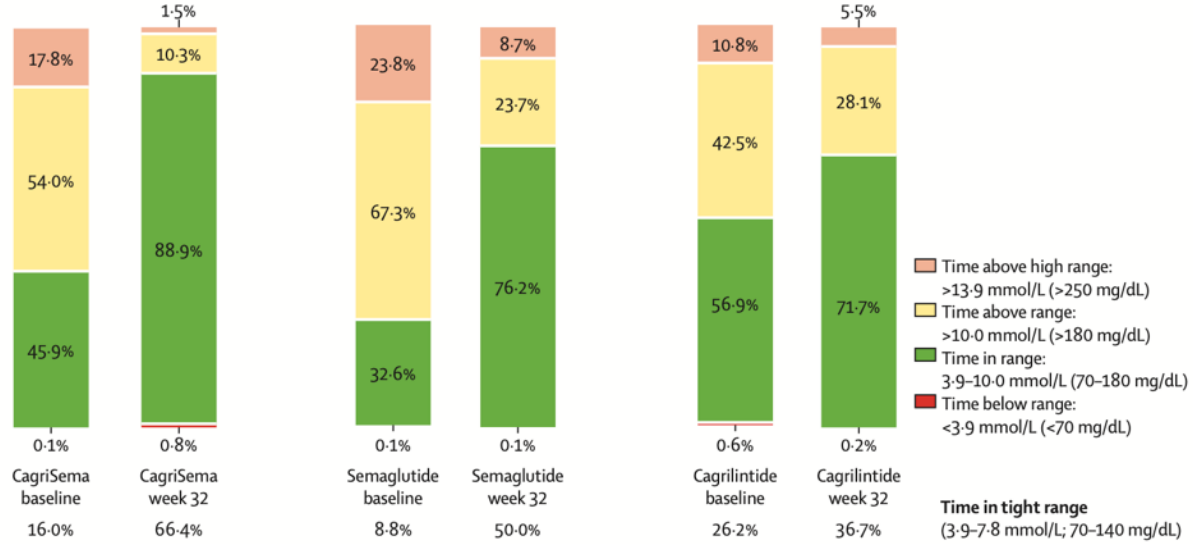
Semaglutide
2.4 mg/sett

Cagrilintide
2.4 mg/sett

CagriSema
2.4/2.4 mg sett

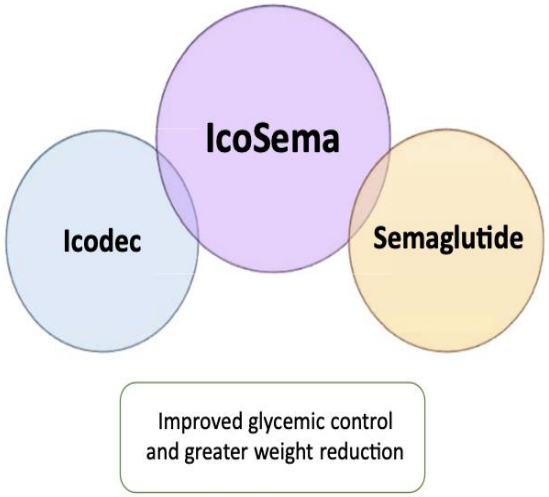






Frias JP et al, Lancet 2023; 402: 720-730

IcoSema



COMBINE 1
Trial fase 3
IcoSema vs Icodec

Outcome primario: variazioni HbA1c
Outcome secondari: variazioni peso corporeo, episodi ipoglicemia (livello 2 e 3)

COMBINE 2
Trial fase 3
IcoSema vs Semaglutide 1 mg/sett

Outcome primario: variazioni di HbA1c
Outcome secondari: variazioni di FPG, peso corporeo, episodi ipoglicemia (livello 2 e 3)

COMBINE 3
Trial fase 3
IcoSema vs Glargine e Aspart

Outcome primario: variazioni HbA1c
Outcome secondari: variazioni peso corporeo, TIR, TAR, TBR, dose insulina totale settimanale, episodi ipoglicemia (livello 2 e 3), DTSQs

Risultati (IcoSema vs basal-bolus)
HbA1c media -1.47% vs -1.40%
Peso medio -3.6 kg vs +3.2 kg

COMBINE 4
Trial fase 3
IcoSema vs Glargine

Outcome primario: variazioni HbA1c
Outcome secondari: variazioni peso corporeo, FPG, TIR, TAR, TBR, dose insulina totale settimanale, episodi di ipoglicemia (livello 2 e 3), DTSQs

Seetharaman R et al, J Basic Clin Physiol Pharmacol 2024

Survodutide

NCT04153929
Trial fase 2

GCGR agonism
- ↑ Energy expenditure
- ↑ Fatty acid oxidation
- ↑ Lipolysis

Survodutide
GCGR/GLP-1R dual agonist

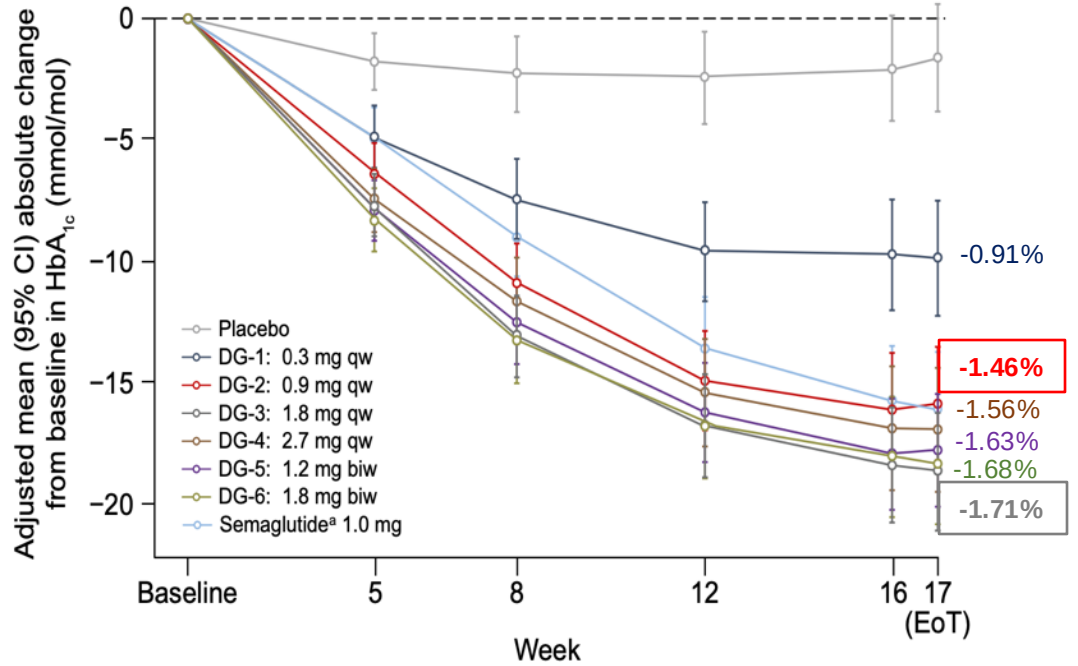
GLP-1R agonism
- ↓ Gastric emptying
- ↓ Food intake/ appetite
- ↑ Glucose-dependent insulin secretion

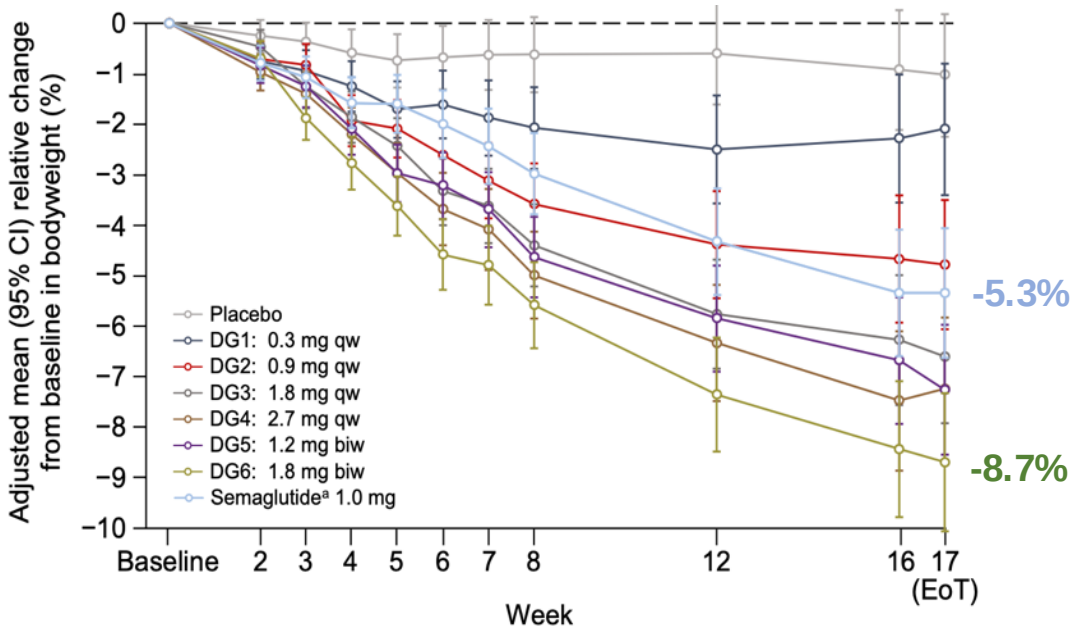
- Type 2 diabetes
- HbA_{1c} 53–86 mmol/mol
- Age 18–75 years
- BMI 25–50 kg/m²
- Background metformin

Received:

- Placebo
- Survodutide 0.3 mg qw
- Survodutide 0.9 mg qw
- Survodutide 1.8 mg qw
- Survodutide 2.7 mg qw
- Survodutide 1.2 mg biw
- Survodutide 1.8 mg biw
- Semaglutide 1.0 mg qw

16 weeks

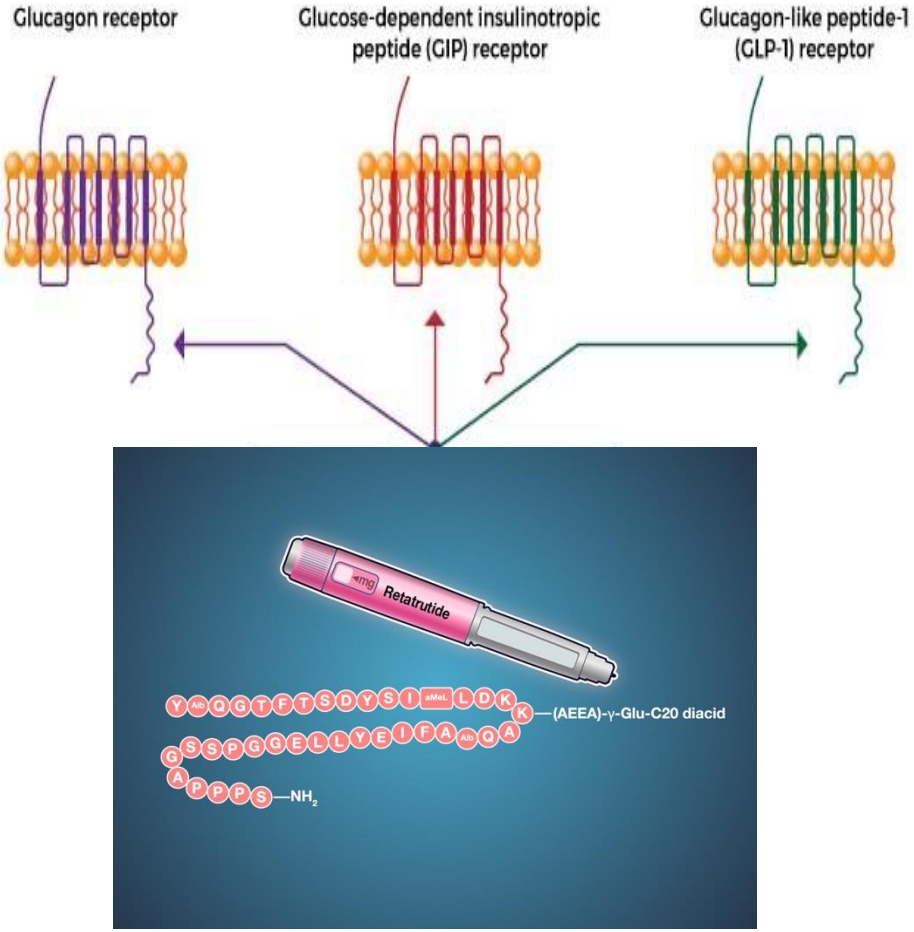




Bluher M et al, Diabetologia 2023; 67: 470-482

Retatrutide

NCT04867785
Trial fase 2



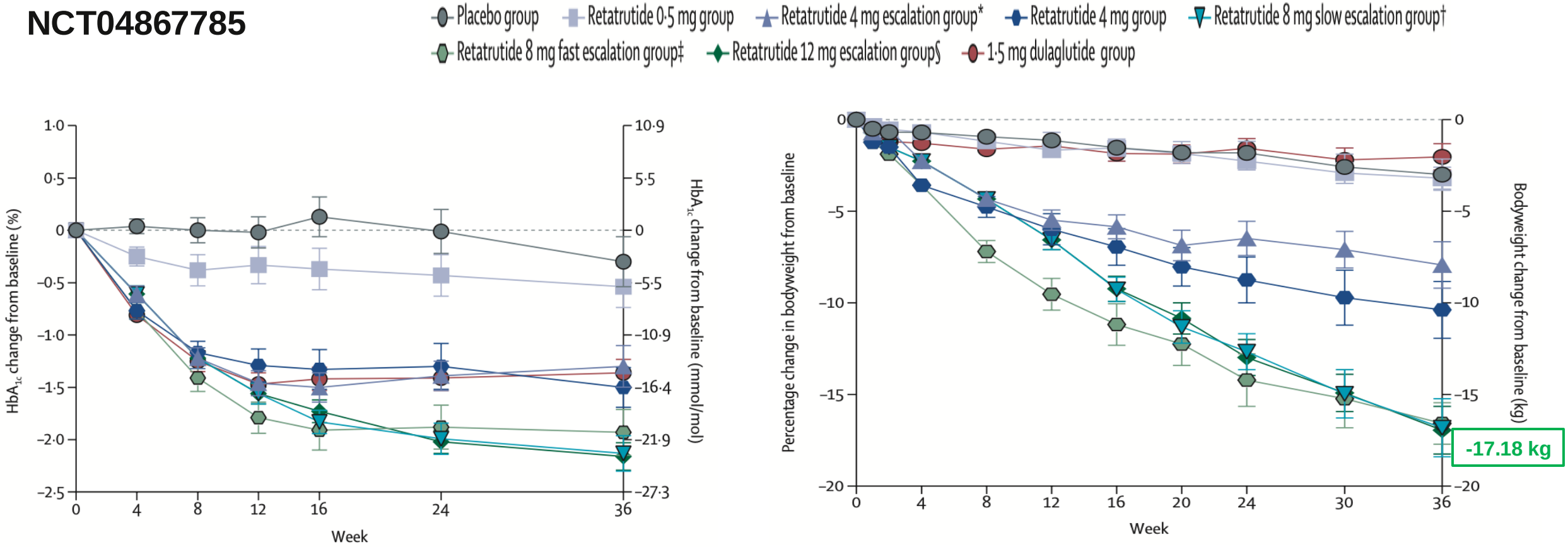
275 pazienti con DM2
HbA1c media 8.3 ± 1.1%
BMI medio 35 ± 6.3 kg/m^2

- Placebo
- Retatrutide 0.5 mg/sett
- Retatrutide 4 mg/sett EG
- Retatrutide 4 mg/sett
- Dulaglutide 1.5 mg/sett
- Retatrutide 8 mg/sett SE
- Retatrutide 8 mg/sett FE
- Retatrutide 12 mg/sett EG

Rosenstock J et al, Lancet 2023; 402: 529-544

Retatrutide

NCT04867785



	36 settimane	Vs placebo	Vs Dulaglutide 1.5 mg/sett
Retatrutide 12 mg	**-2.16 ± 0.13%**	**-1.85%**	**-0.80%**
Placebo	-0.30 ± 0.24%		
Dulaglutide 1.5 mg/sett	-1.36 ± 0.13%		

Rosenstock J et al, Lancet 2023; 402: 529-544

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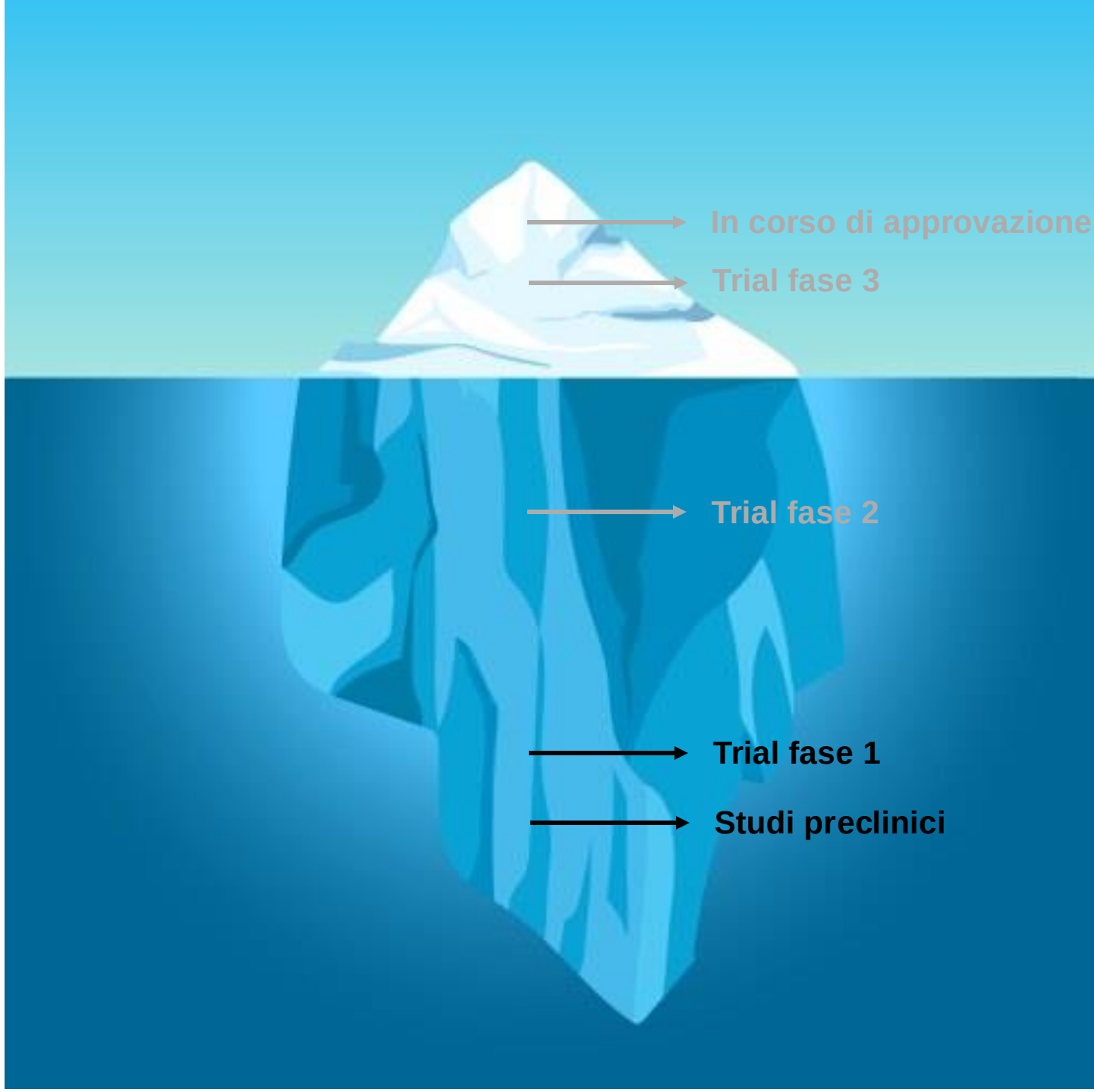
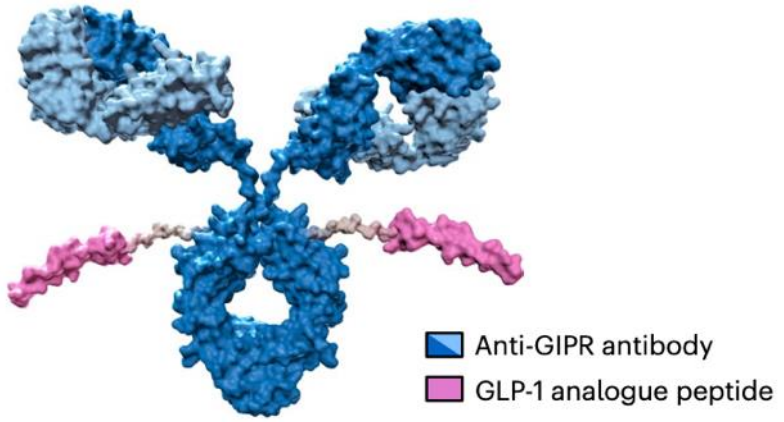
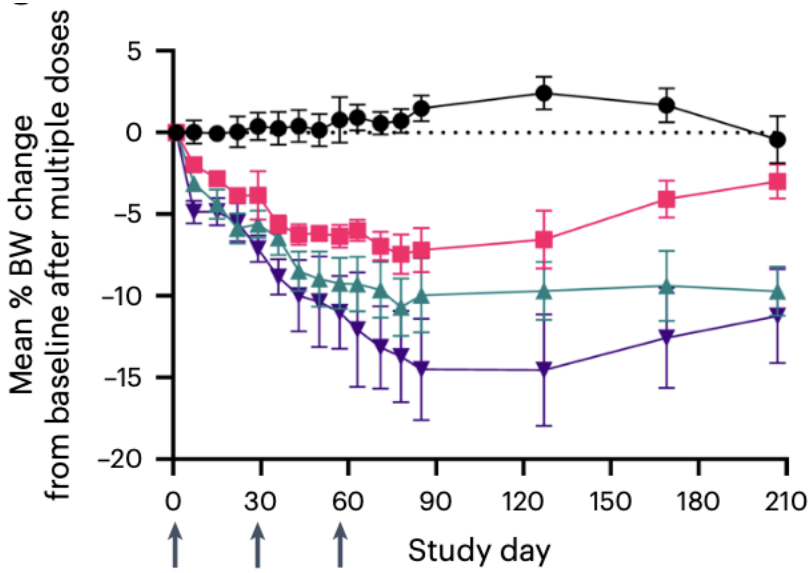


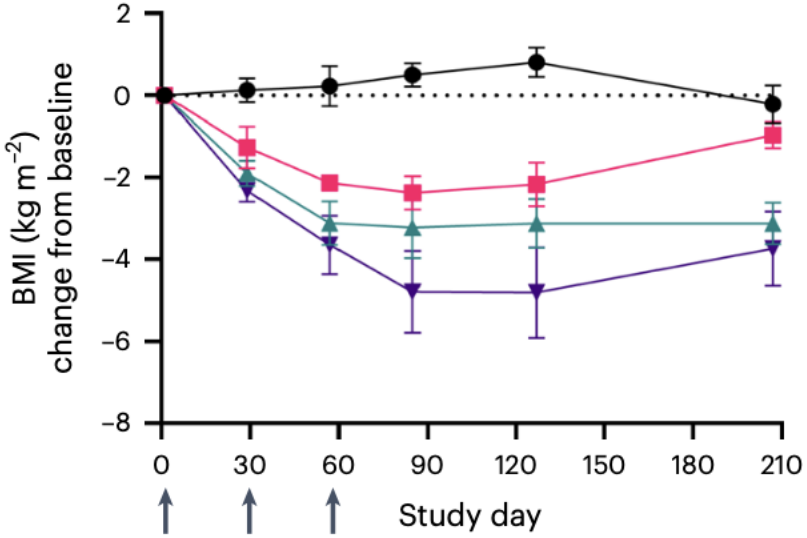
MariTide (AMG 133, Maridebart/Cafraglutide)

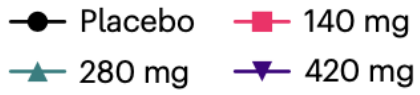
NCT04478708
Trial fase 1

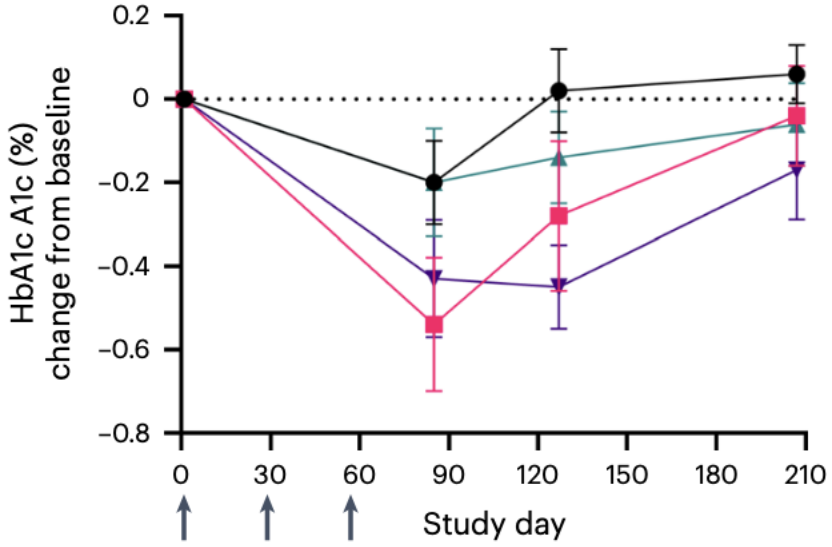


75 pazienti, HbA1c ≤ 6.5%,
BMI 30-40 kg/m^2





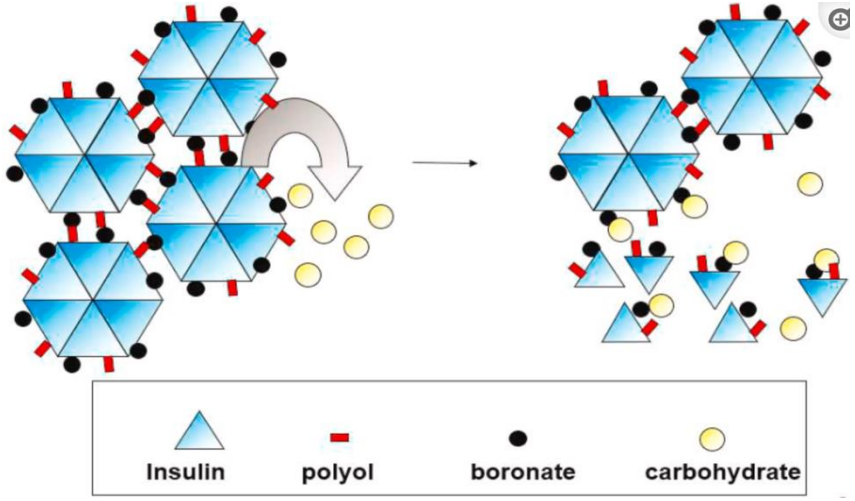




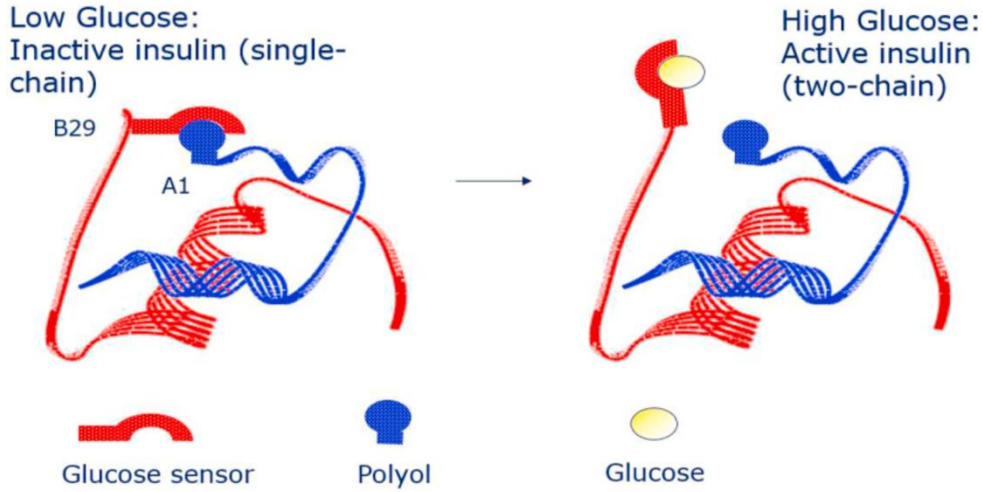
Véniant MM et al, Nature Metabolism 2024; Vol 6: 290-303

Glucose-sensitive insulin

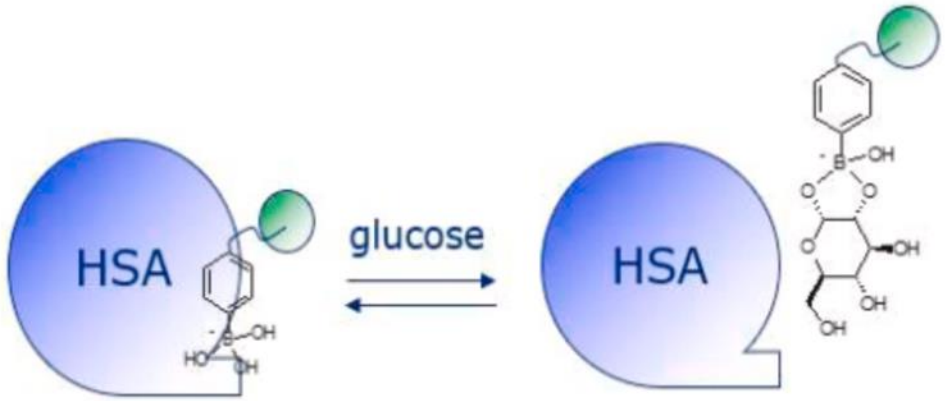
Preparato insulinico «ingegnerizzato» per autoregolare l'attività biologica dell'insulina sulla base delle fluttuazioni glicemiche



Multiesameri insulinici carboidrato-sensibili



Attivazione insulinica con switch molecolare

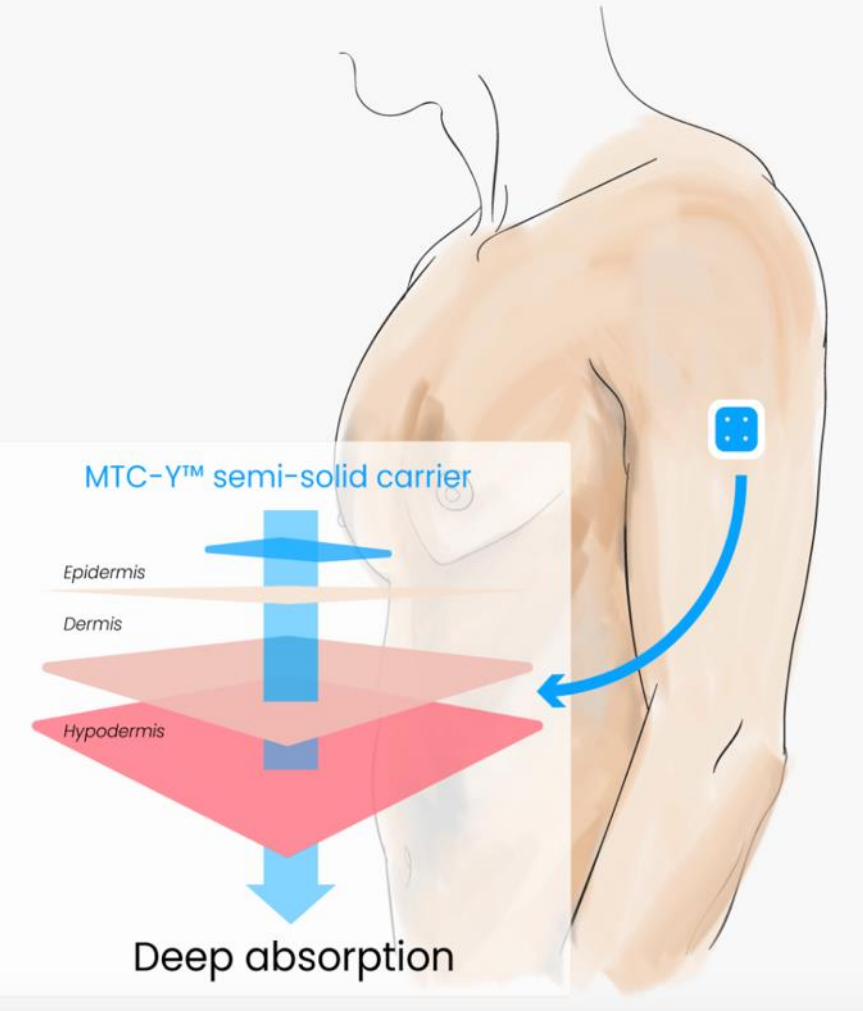


Albumin-binding insulina diboronato

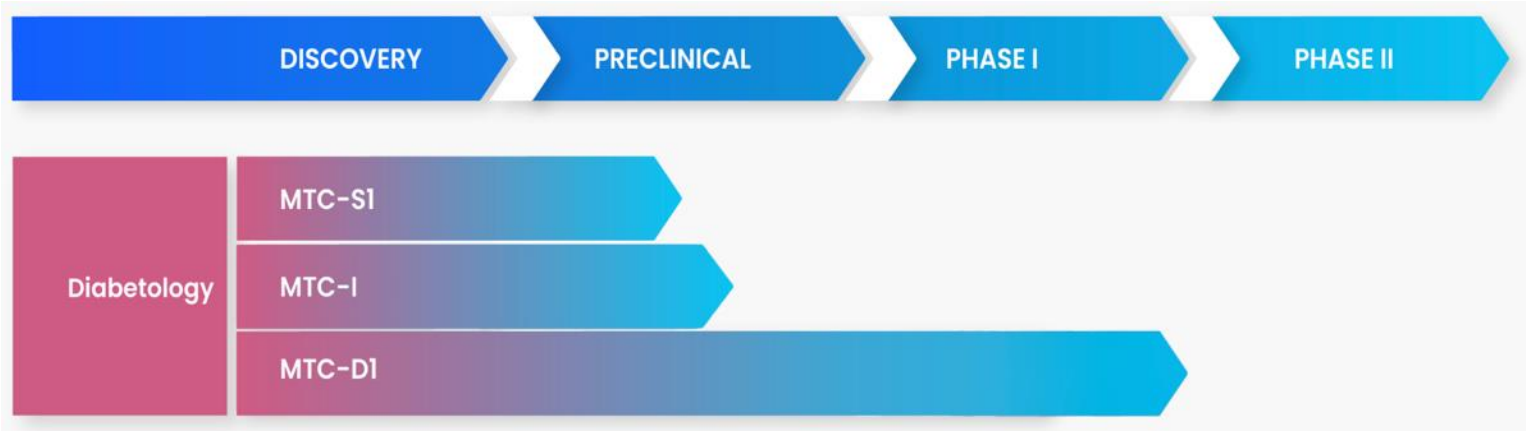
Hoeg-Jensen T et al, Mol Metab 2021; 46: 101-107

Transdermal Drug Delivery (TDD)

MTC-Y: Semisolid emulsion that stimulates transportation through skin



- Non-invasive (no microneedle, no device);
- Larger molecules (proteins, peptides);
- Both lipophilic and hydrophilic;
- Versatile toolkit.

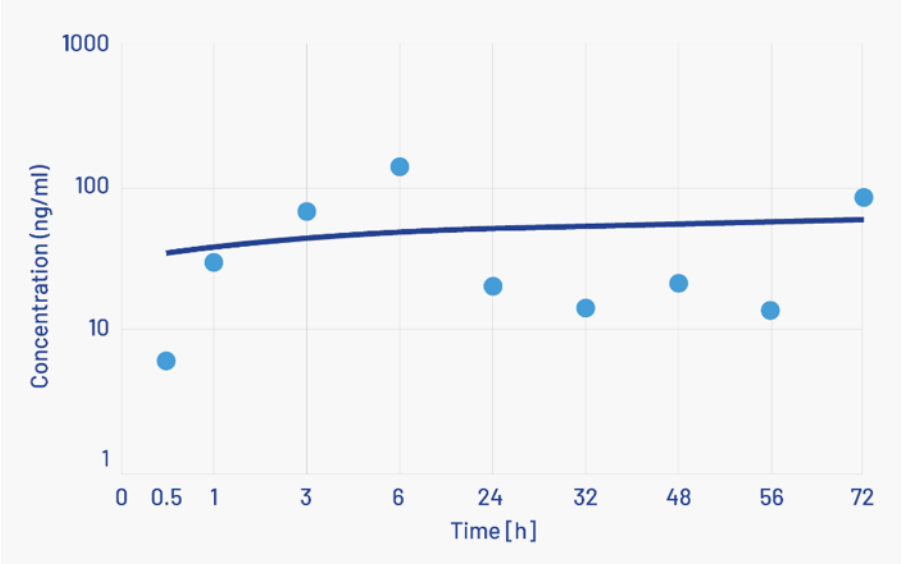


MTC-S1 e MTC- I

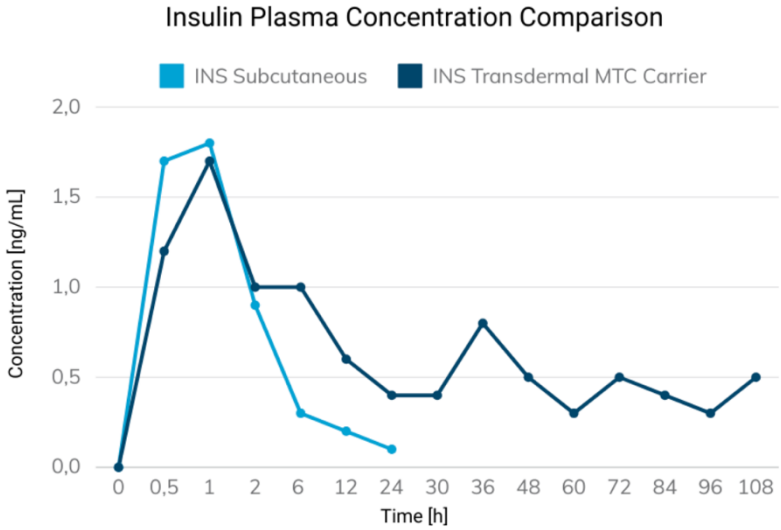
- SC injection (**semaglutide 0,3 mg/kg**)
- MTC-S1 ointment (**semaglutide 2,0 mg**)

- Insulin SC (**Gensulin N – 0.035 mg**)
- MTC Carrier (**insulin – 0.36 mg**)

MTC-S1



MTC-I



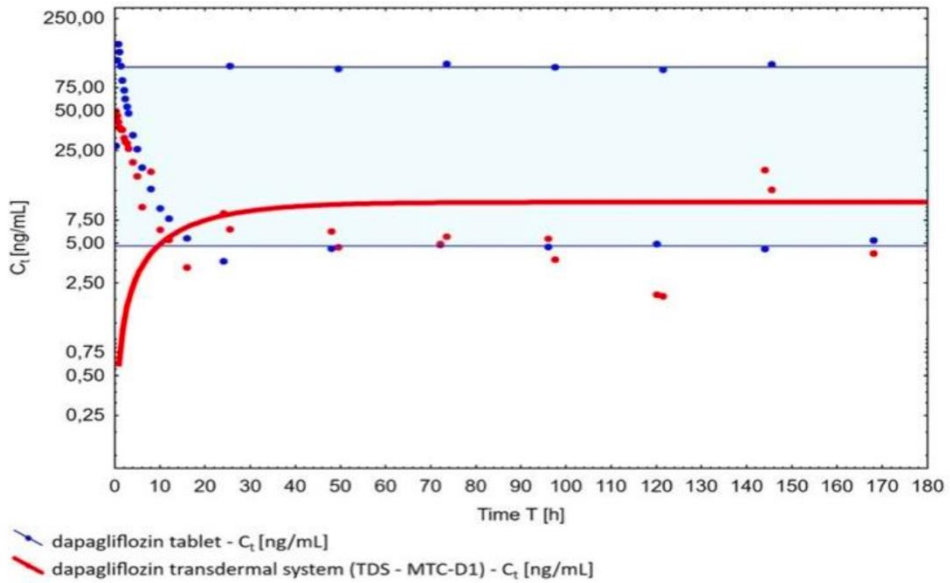
1.Bioavailability of **4% for semaglutide, 55.1% for Insulina**.
2.Constant dosage for semaglutide.
3.Sustained release for insulin.

MTC-D transdermal Dapagliflozin

Trial fase 1

- Oral Dapagliflozin (daily dose for a week)
- Transdermal Dapagliflozin (MTC-D) for a week

- Oral Dapagliflozin
- MTC-D for a week



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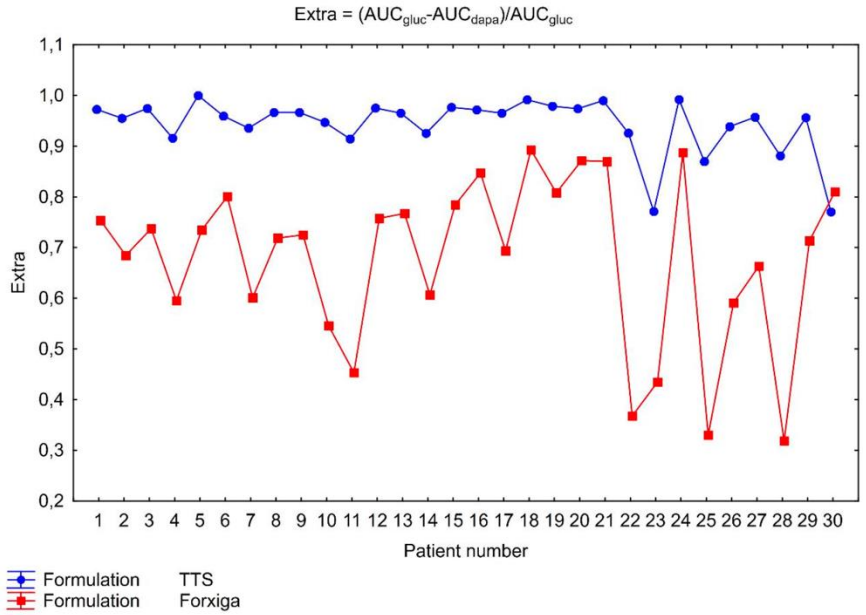
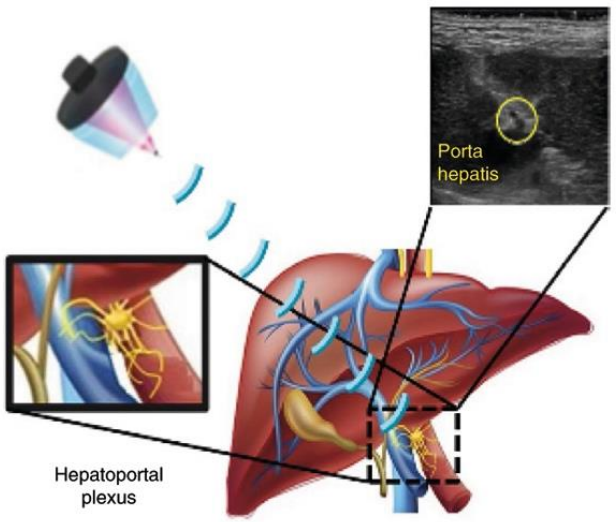
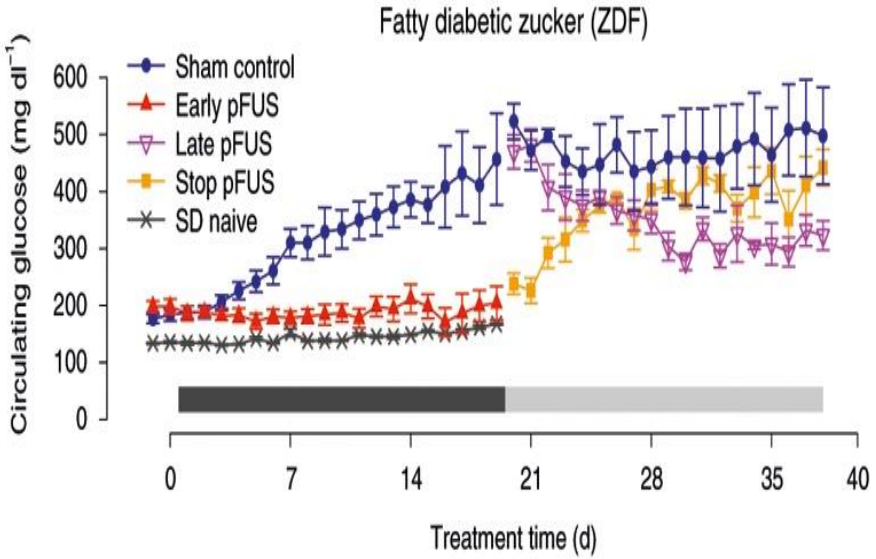


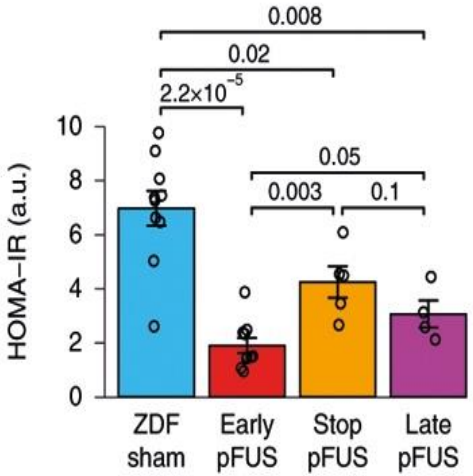
1. **Safety** of the MTC-Y carrier in Human
2. Blood concentration levels closely mirroring those achieved with oral administration
3. **Similar pharmacokinetic profiles**

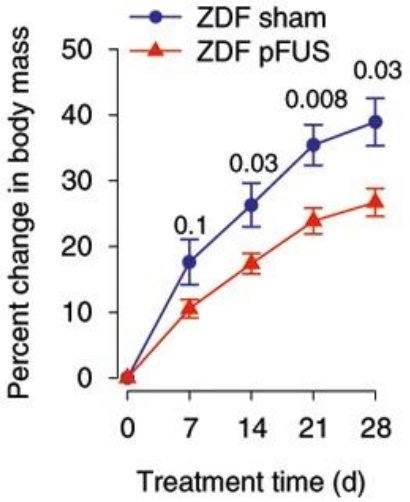
Meler J et al, ATTD 2024

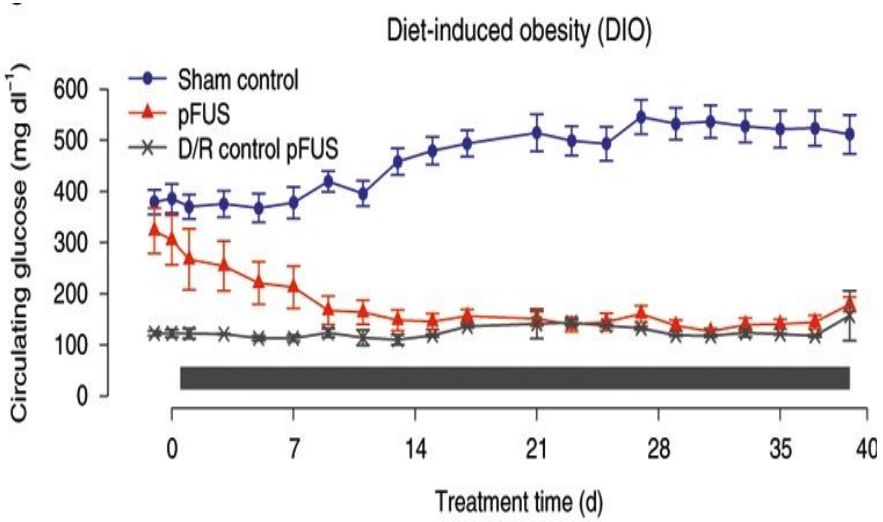
Peripheral Focused UltraSound (pFUS)

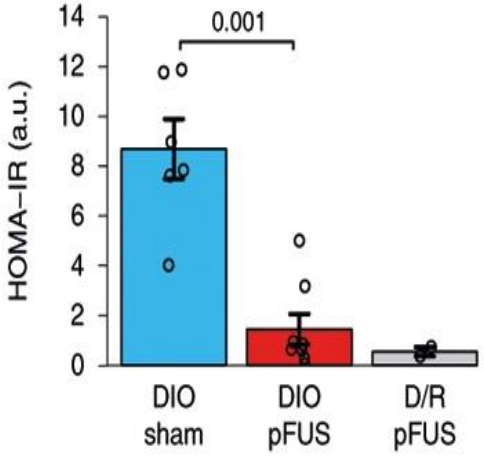


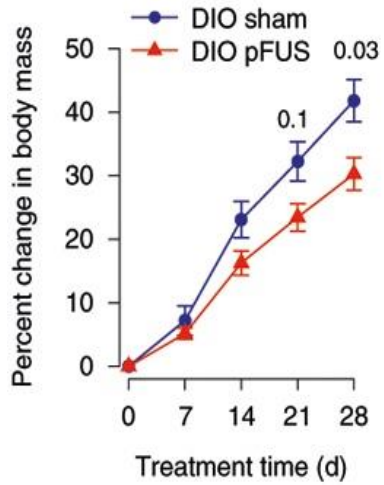












Nuovo futuro approccio per DMT2 e Obesità

Cotero V et al, Nat Biomed Eng 2022; 6(6) : 683-705

GLP-1 Pancreatic Gene Therapy (PGTx)

Terapia genica adenovirus-mediata in grado di indurre produzione duratura a livello insulare di GLP-1

Semaglutide sc
10 nmol/kg/die per 4 sett

Terapia genica
placebo

Terapia genica
one shot

Semaglutide
placebo

Riduzione massa grassa PGTx vs Semaglutide
-21% vs -16%
Riduzione massa magra PGTx vs Semaglutide
-5% vs -5%
Riduzione FG PGTx vs Semaglutide
-18% vs -18%

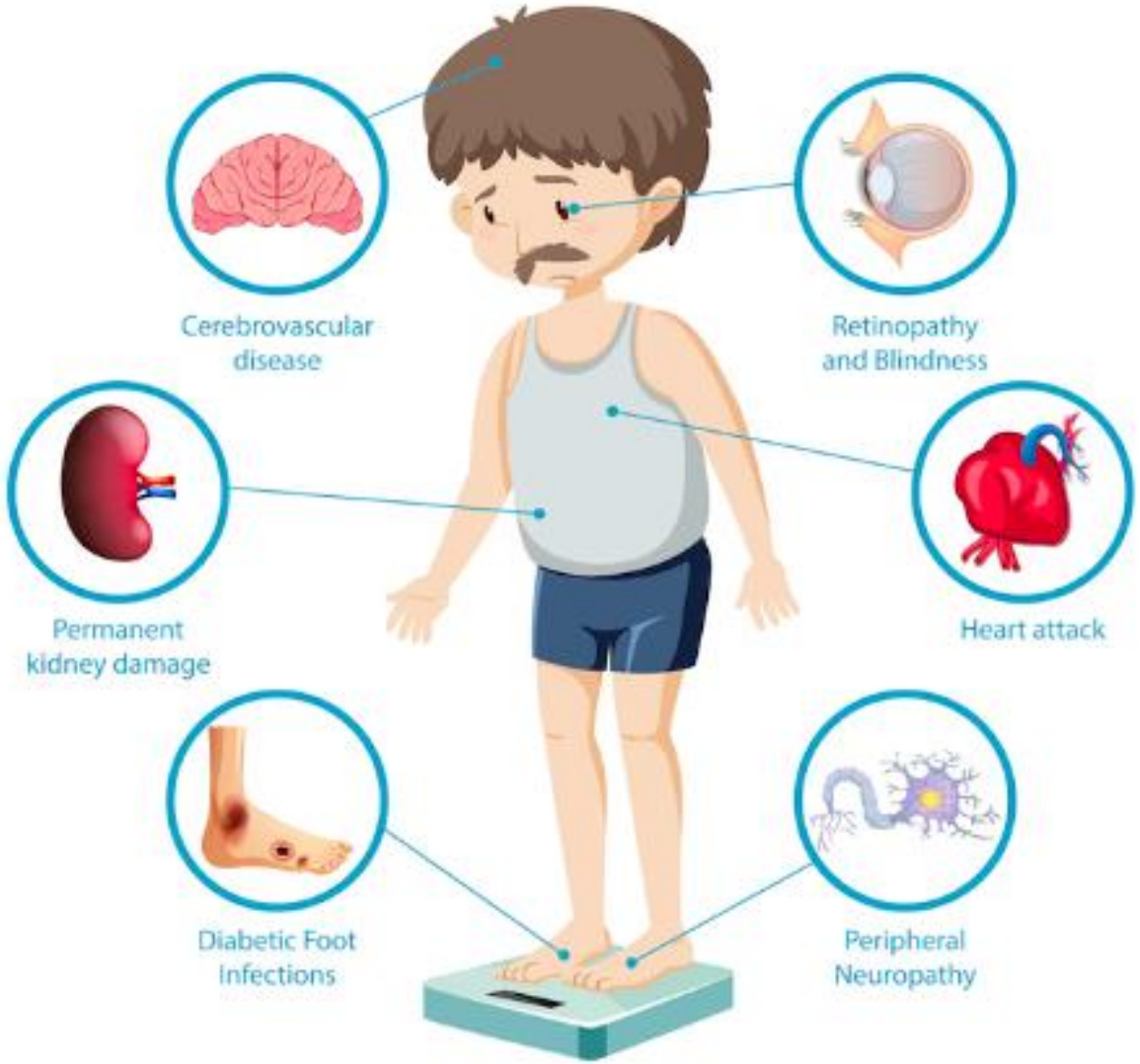
4 sett dopo sospensione Semaglutide
Massa grassa -1% vs baseline
Massa magra -2% vs baseline

Sospensione semaglutide e switch PGTx
Massa grassa -17% vs baseline
Massa magra -5% vs baseline

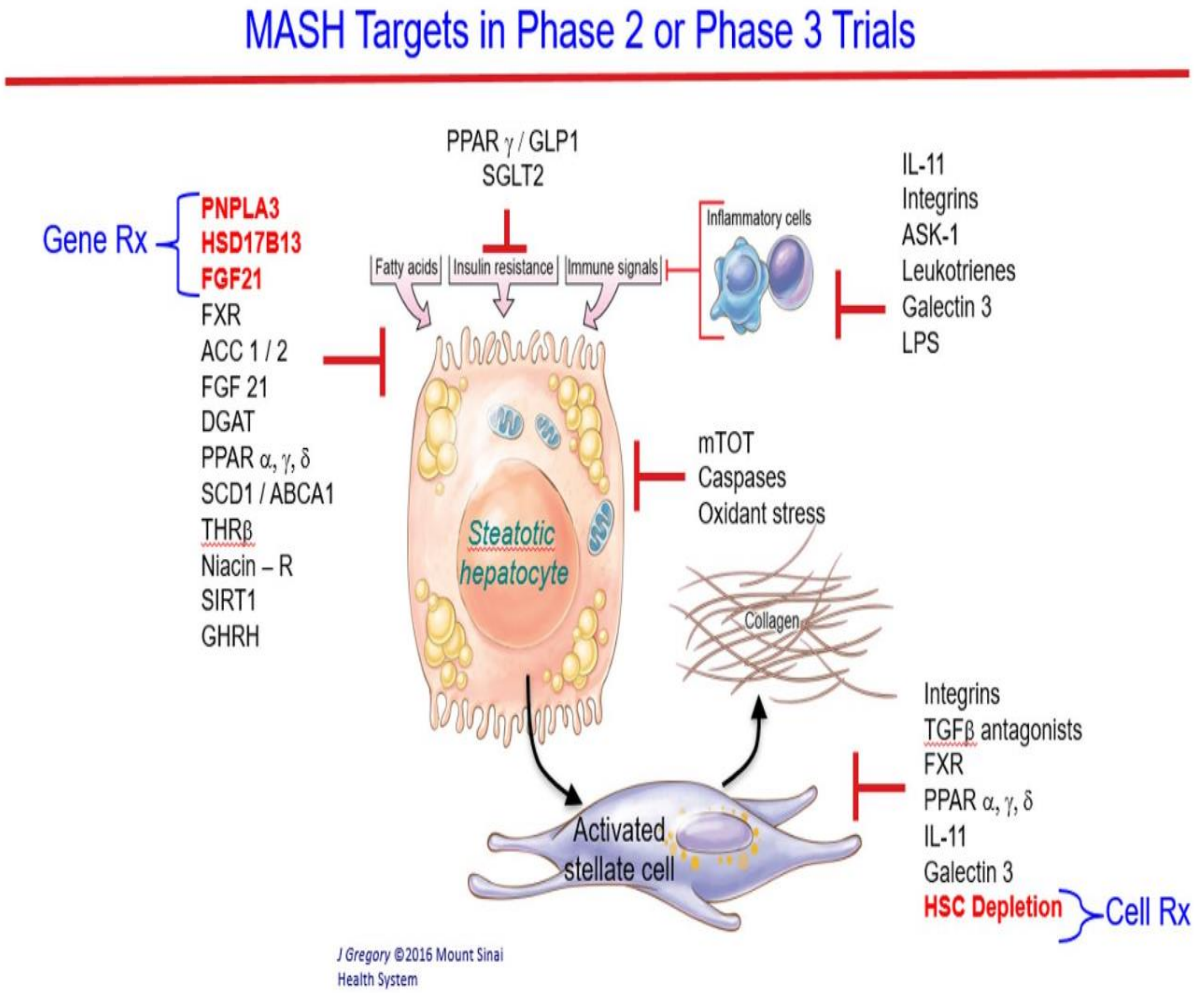
Fitzpatrick AL et al. Diabetes 2024; 73: 261

Agenda

- Futuro a breve termine
- Futuro a medio termine
- Futuro a lungo termine
- Futuro delle complicanze



MASLD



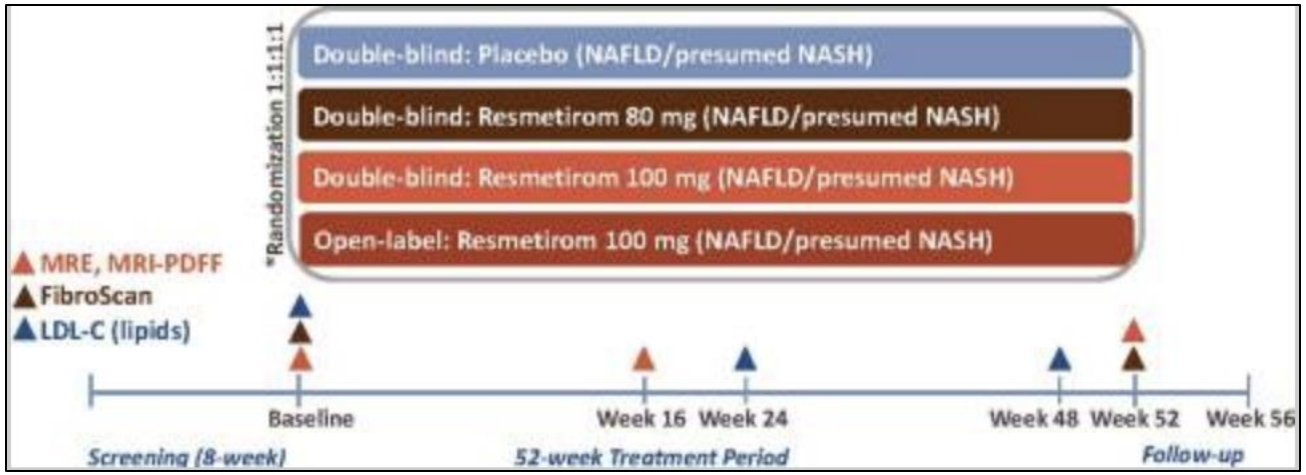
Drug	Mechanism of action	Use
Obeticholic acid	Targets farnesoid X receptor axis [43]	PBC and MAFLD MALFD trials halted by FDA
Resmetirom	Thyroid beta-agonists	MAFLD Pending FDA approval
Aramchol	Hepatic stearoyl-CoA desaturase inhibitor	HIV, Gallstones, MAFLD Studies halted
Probiotics/prebiotics/synbiotics	MTT	Digestion, immune health, MAFLD Data pending
Pegozafermin	Fibroblast growth factor analog	Severe hypertriglyceridemia and MAFLD Data pending
Non-coding RNAs	Regulating gene transcription	Cancer, diabetes, obesity, liver diseases, e.g., MAFLD Data pending
CAR T cells	Target and eliminate uro-kinase-type plasminogen activator receptor hepatic stellate cells and macrophages, reducing fibrosis	Hematologic malignancies and MAFLD Data pending

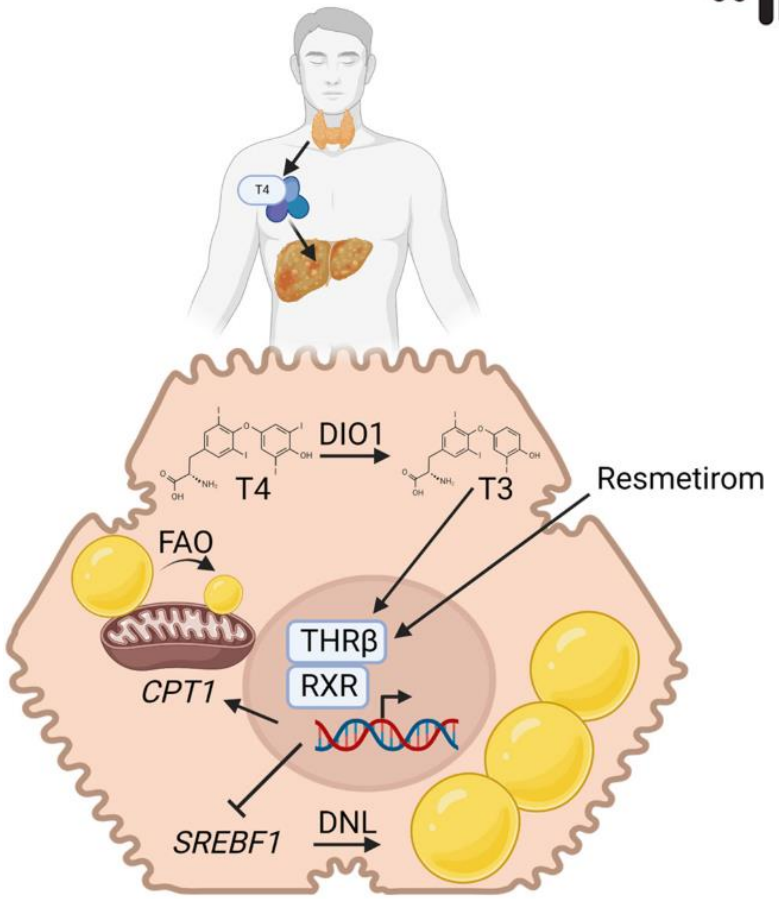
Gish R et al, Hepatology International 2024

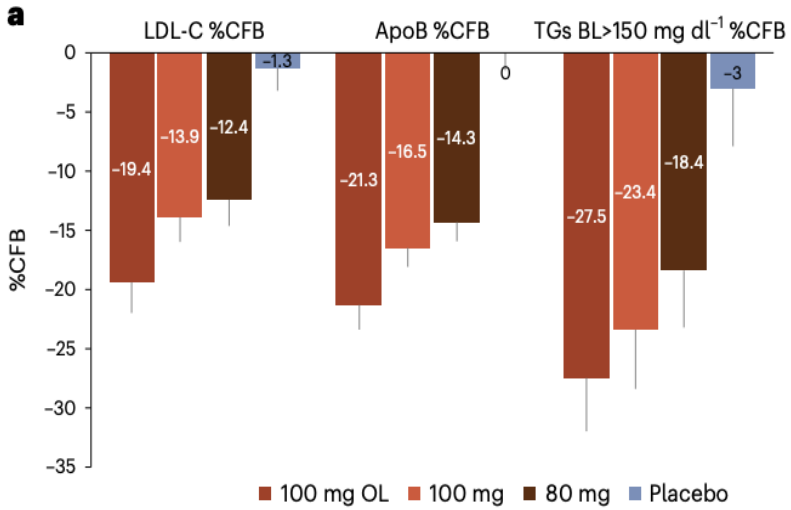
MASLD - Resmetirom

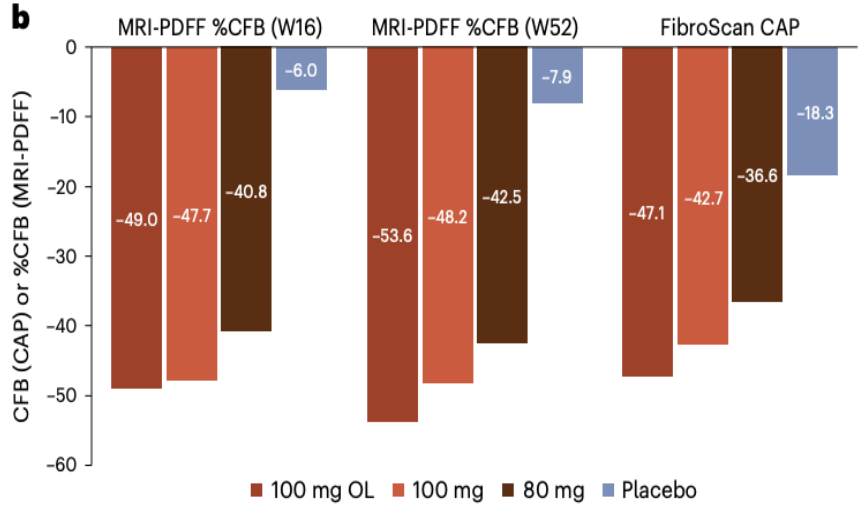
Agonista selettivo THR-β

MAESTRO-NAFLD-1
Trial fase 3







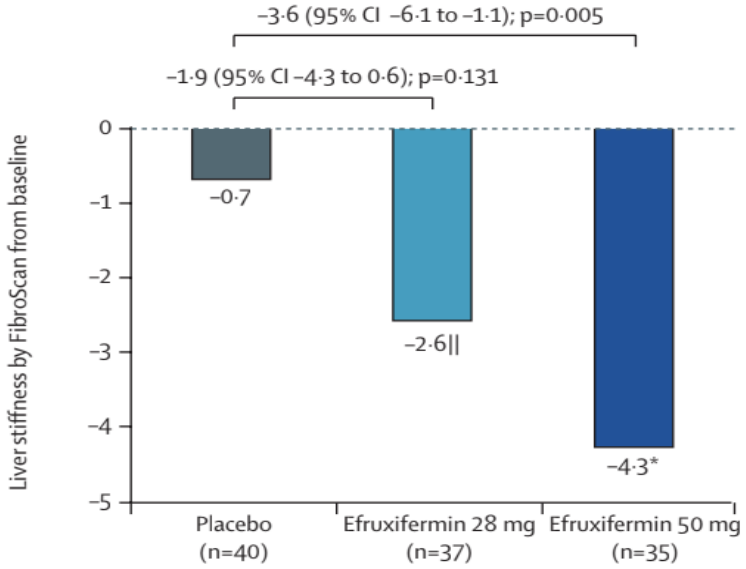


Harrison SA et al, Nature Medicine 2023; Vol 29: 2919-2928

MASLD – analoghi LA di FGF-21

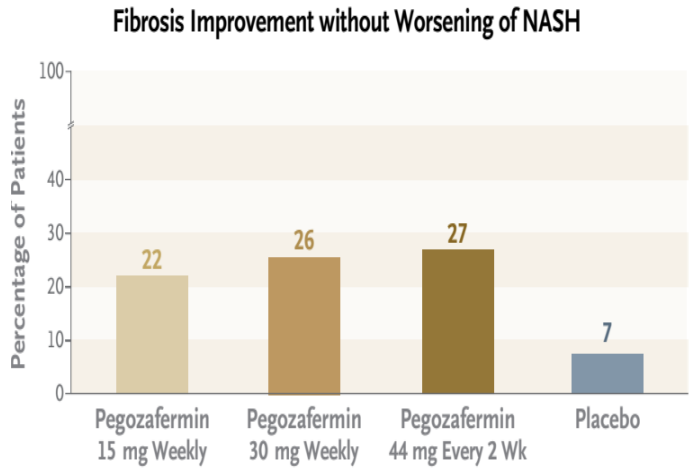
Efruxifermin (EFX)
HARMONY
Trial fase 2b

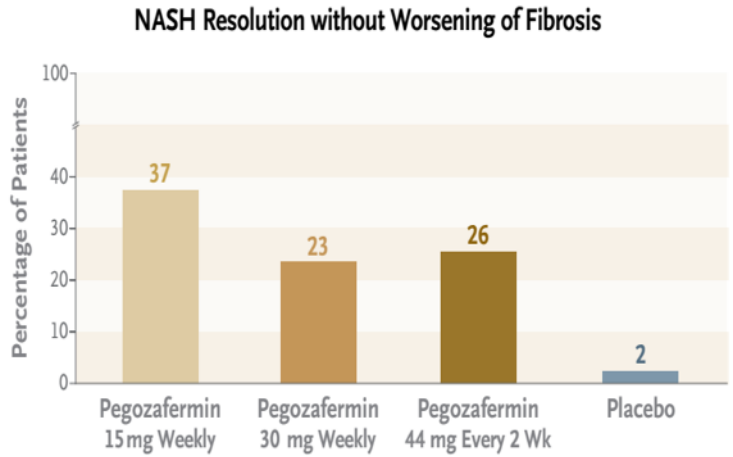
128 pazienti, MASH (biopsia),
fibrosi F2-F3



Pegozafermin
ENLIVEN
Trial fase 2b

219 pazienti, MASH (biopsia),
Fibrosi F2-F3





Harrison SA et al, Lancet Gastroenterol Hepatol 2023; 8(12): 1080-1093

Loomba R et al, N Engl J Med 2023; 389(11): 998-1008

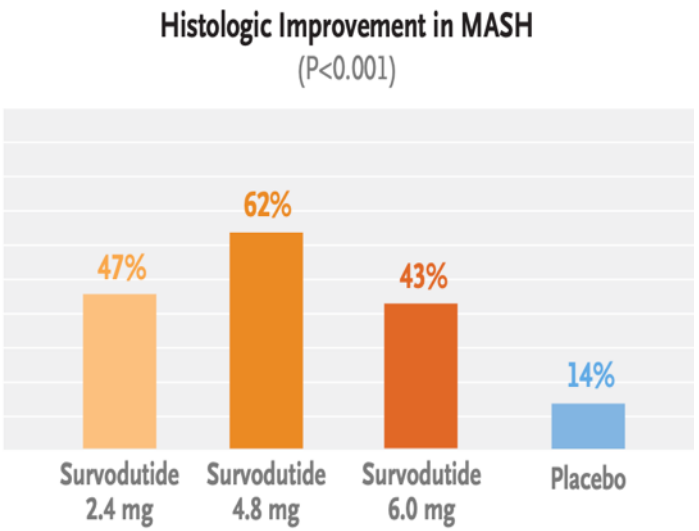
MASLD – Survodutide e Tirzepatide

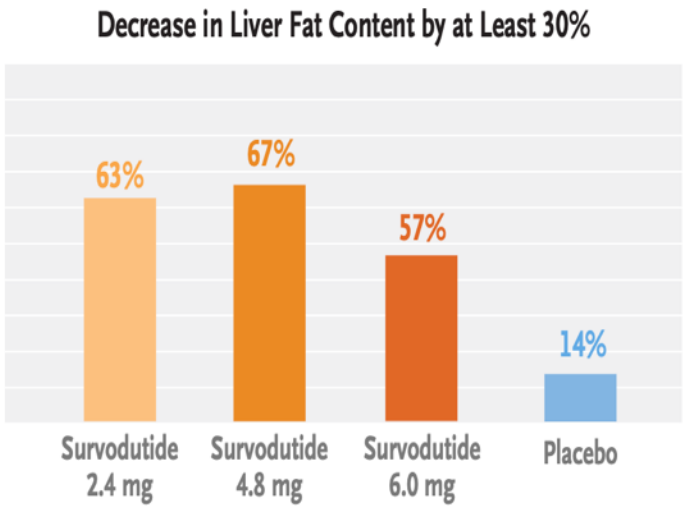
NCT04771273
Trial fase 2

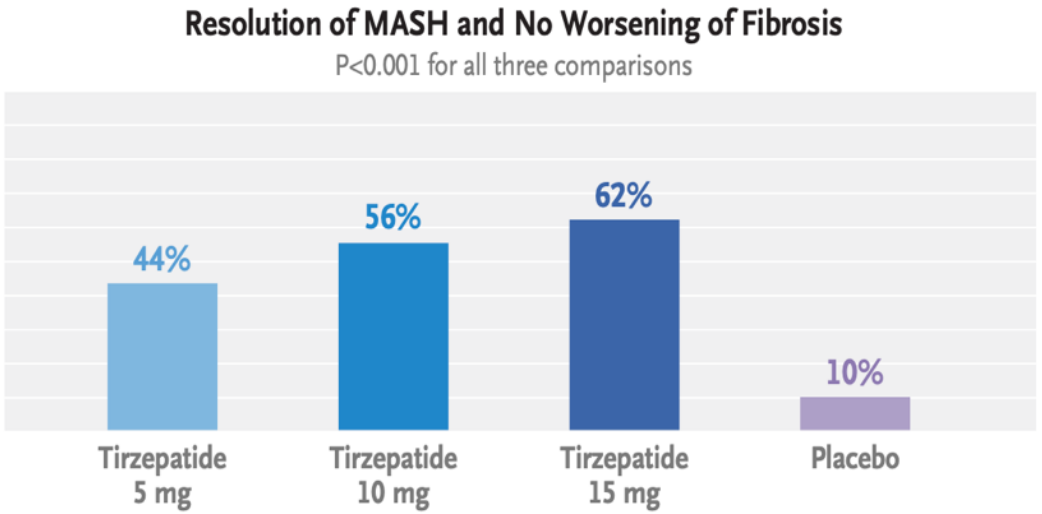
293 pazienti, MASH confermata da biopsia, fibrosi stadio F1-F3

SYNERGY-NASH
Trial fase 2

190 pazienti, MASH confermata da biopsia, fibrosi stadio 2 o 3

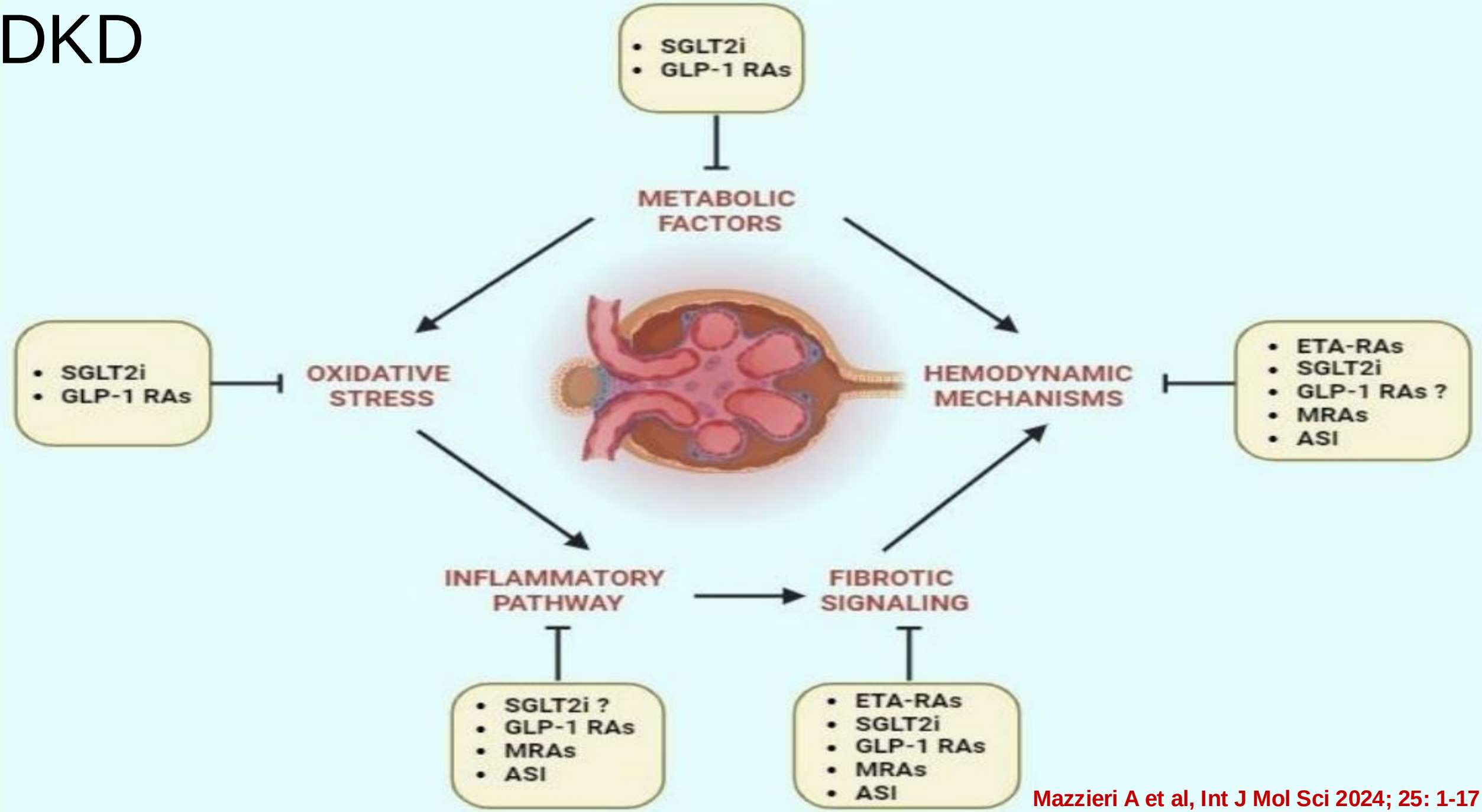






Sanyal AJ et al, N Engl J Med 2024; 391: 311-319
Loomba R et al, N Engl J Med 2024; 391: 299-310

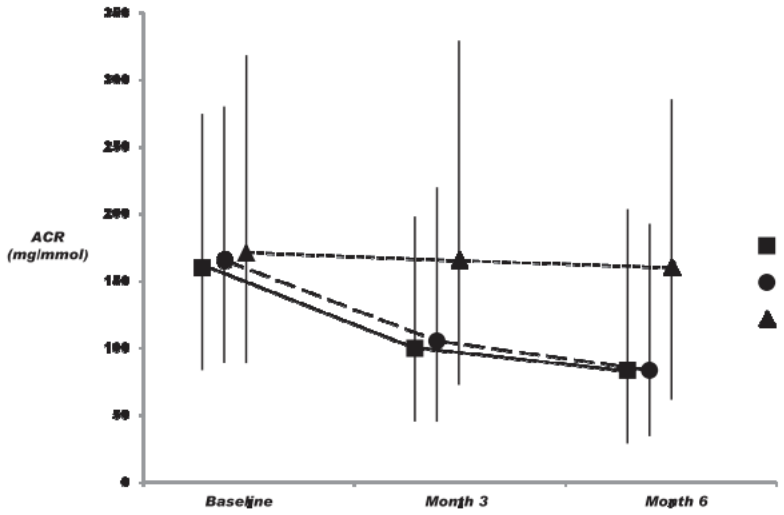
DKD



Mazzieri A et al, Int J Mol Sci 2024; 25: 1-17

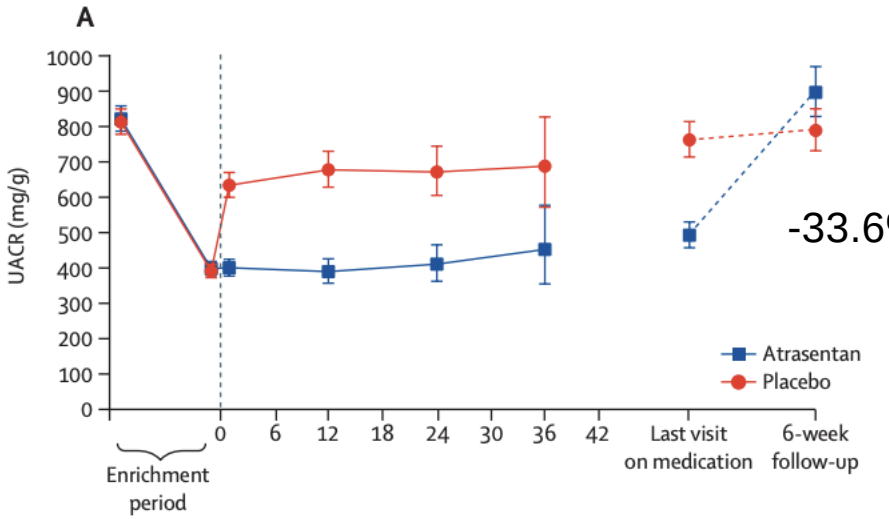
DKD - Antagonisti recettoriali ET-1 (ETA-RAs)

Avosentan
ASCEND
Trial fase 3



-44% vs placebo
-49% vs placebo

Atrasentan
SONAR
Trial fase 3



-33.6% vs placebo

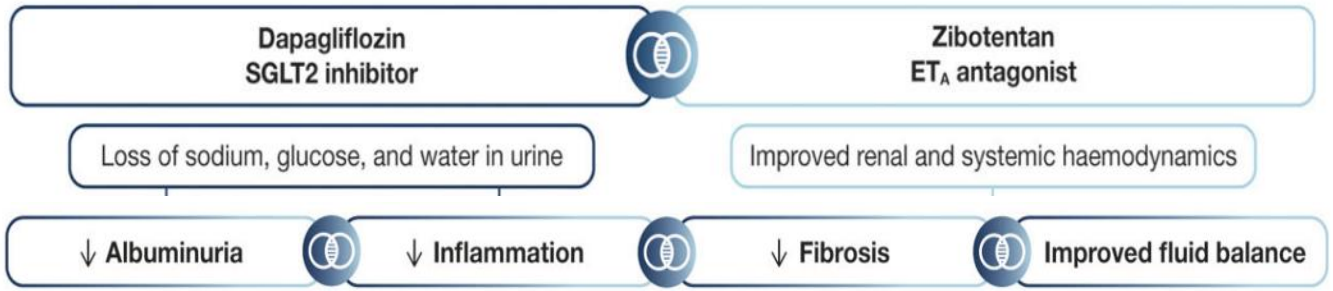
↑ Ritenzione fluidi
↑ Eventi di scompenso cardiaco congestizio
Anemia

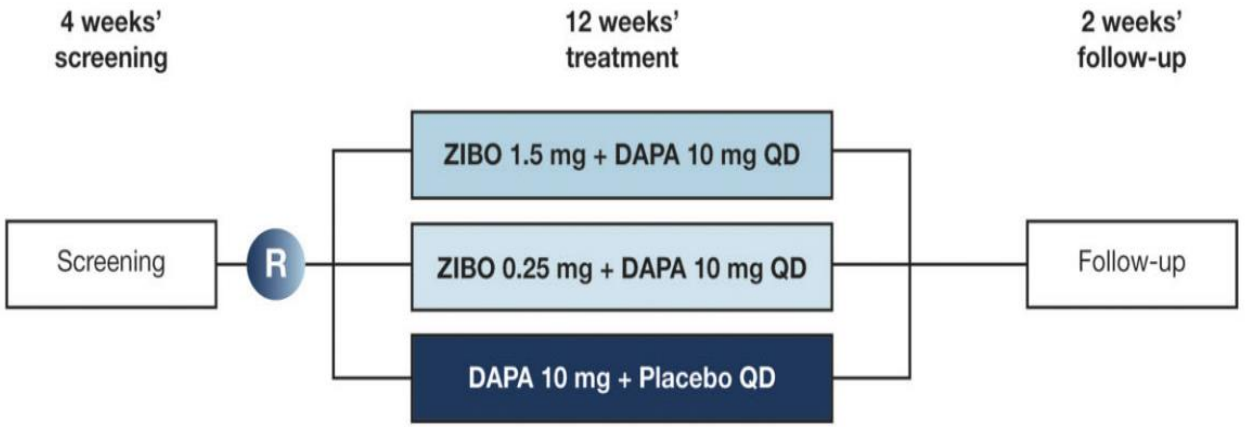
Mann JFE et al, J Am Soc Nephrol 2010; 21: 527-535

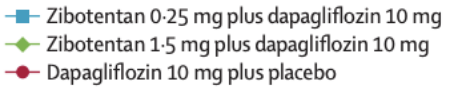
Heerspink HJL et al, Lancet 2019; 393: 1937-1947

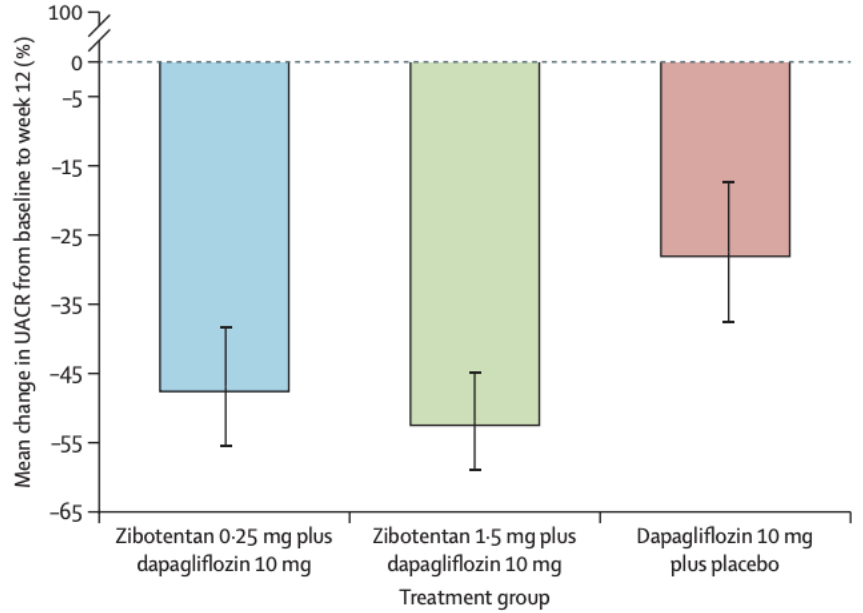
DKD - Antagonisti recettoriali ET-1 (ETA-RAs)

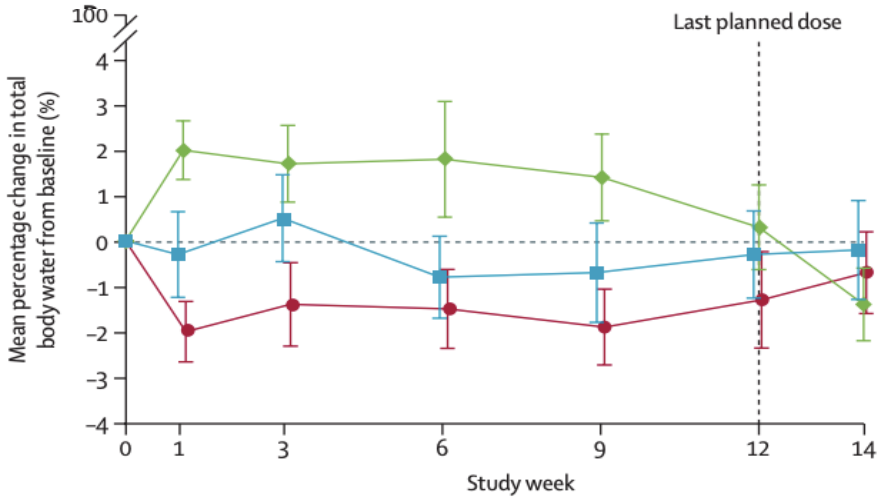
Zibotentant + Dapagliflozin
ZENITH-CKD
Trial fase 2







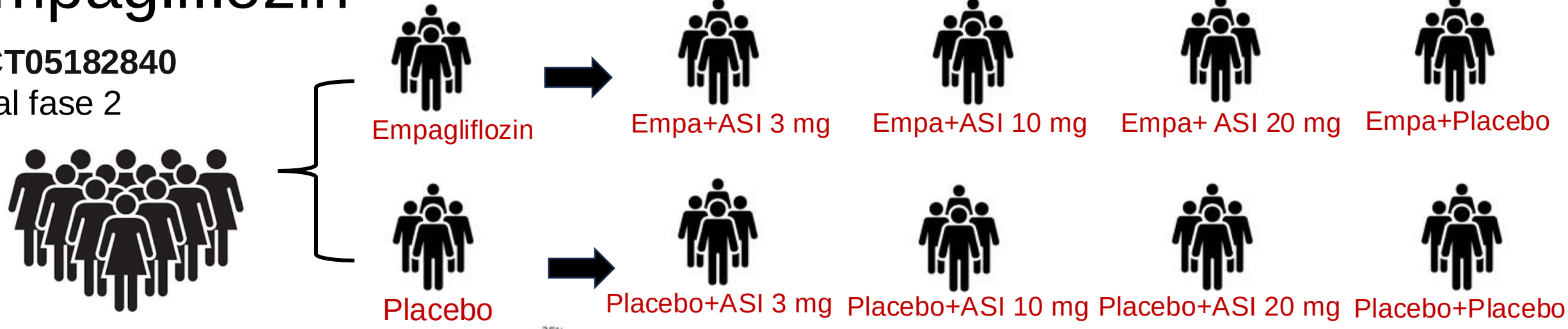


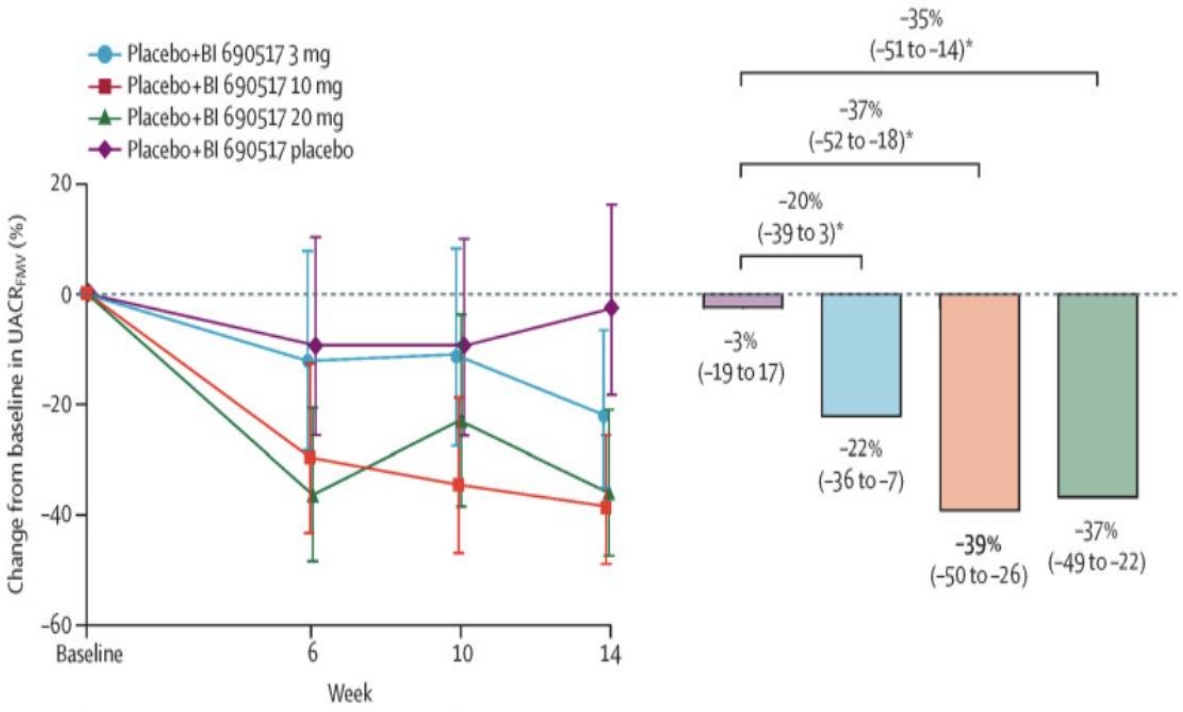


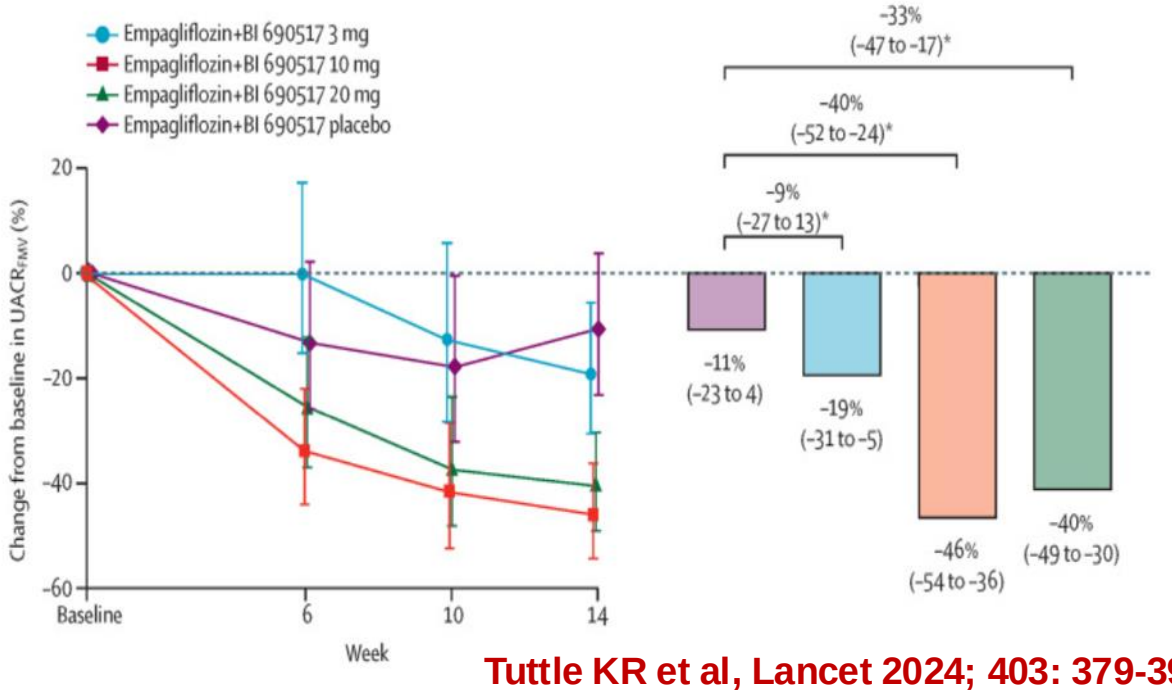
Heerspink HJL et al, Nephrol Dial Transplant 2024; 39: 415-425
Heerspink HJL et al, Lancet 2023; 402: 2004-2017

DKD – Aldosteron synthase inhibitor (ASI) + Empagliflozin

NCT05182840
Trial fase 2







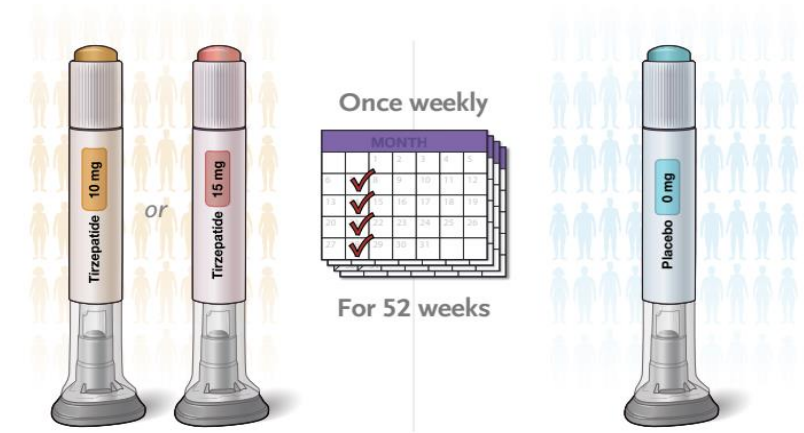
Tuttle KR et al, Lancet 2024; 403: 379-390

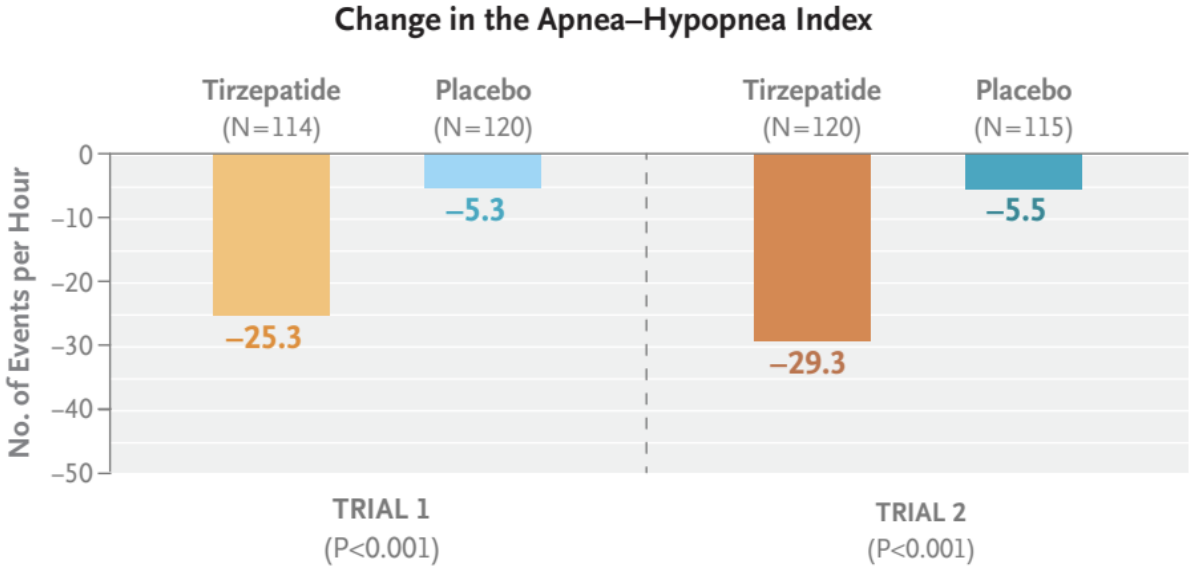
OSAS – Tirzepatide

SURMOUNT-OSA
Trial fase 3

Trial 1
234 pazienti, AHI ≥ 15
NO CPAP

Trial 2
235 pazienti, AHI ≥ 15
CPAP





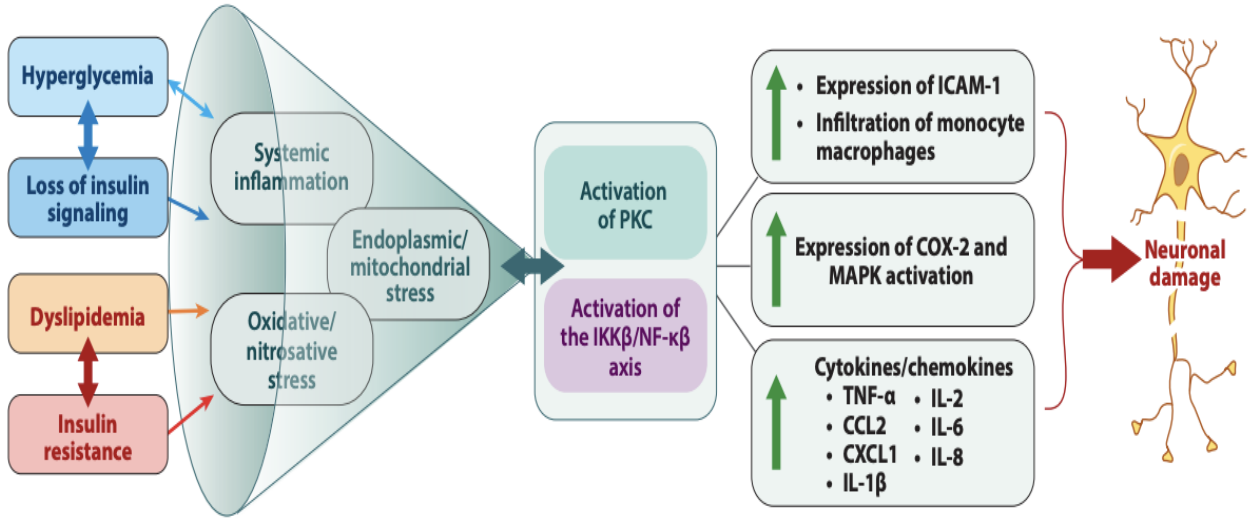
End Point	Trial 1			Trial 2		
	Tirzepatide N=114	Placebo N=120	Estimated Treatment Difference or Relative Risk (95% CI)†	Tirzepatide N=120	Placebo N=115	Estimated Treatment Difference or Relative Risk (95% CI)†
Primary end point						
Change in AHI (95% CI) — no. of events/hr	−25.3 (−29.3 to −21.2)	−5.3 (−9.4 to −1.1)	−20.0 (−25.8 to −14.2)	−29.3 (−33.2 to −25.4)	−5.5 (−9.9 to −1.2)	−23.8 (−29.6 to −17.9)
Key secondary end points						
Percent change in AHI (95% CI)	−50.7 (−62.3 to −39.1)	−3.0 (−16.9 to 10.9)	−47.7 (−65.8 to −29.6)	−58.7 (−69.1 to −48.4)	−2.5 (−16.2 to 11.2)	−56.2 (−73.7 to −38.7)
Reduction of ≥50% in AHI events at wk 52 — no. (%)	70 (61.2)	23 (19.0)	3.3 (2.1 to 5.1)	86 (72.4)	27 (23.3)	3.1 (2.1 to 4.5)
AHI of <5 or AHI of 5 to 14 with ESS ≤10 at wk 52 — no. (%)	48 (42.2)	19 (15.9)	2.9 (1.8 to 4.8)	60 (50.2)	16 (14.3)	3.3 (2.0 to 5.4)

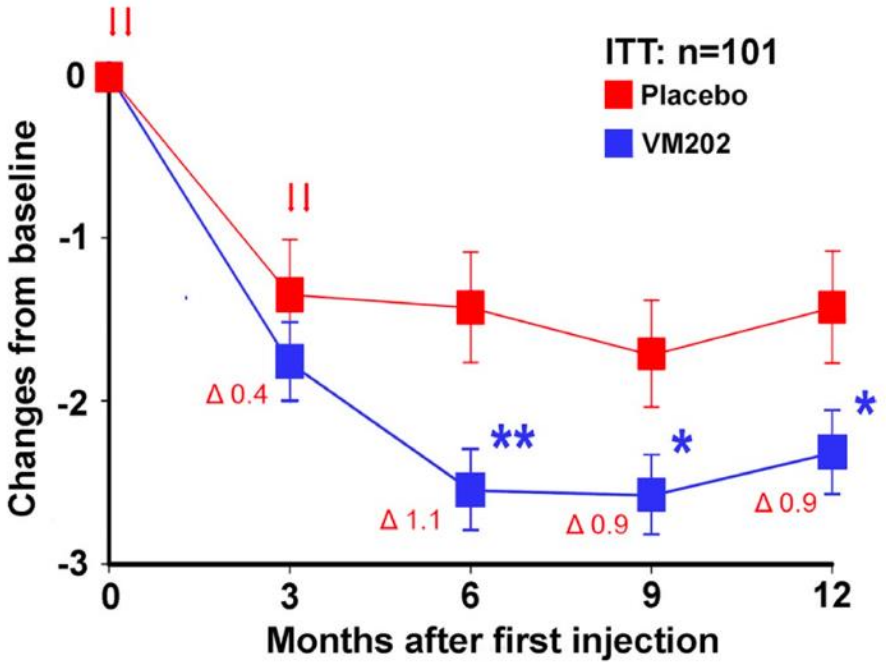
Malhotra A et al, N Engl J Med 2024; 391: 1193-1205

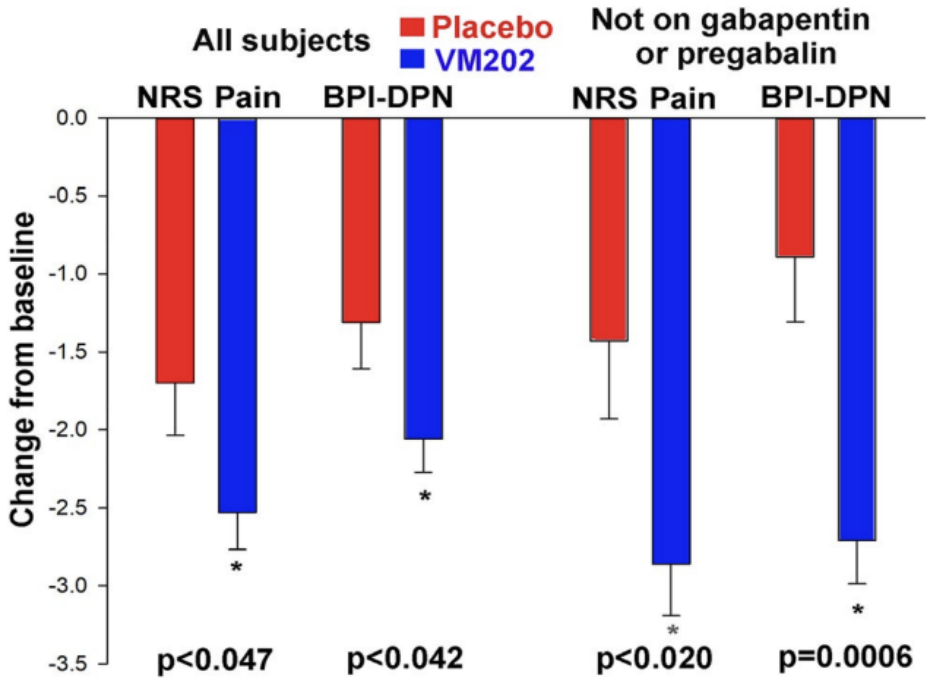
Neuropatia diabetica periferica

VM202
Terapia genica con plasmide per l'espressione di 2 isoforme di HGF con potente attività neurotrofica e angiogenica.

DPN 3-1b
Trial fase 3





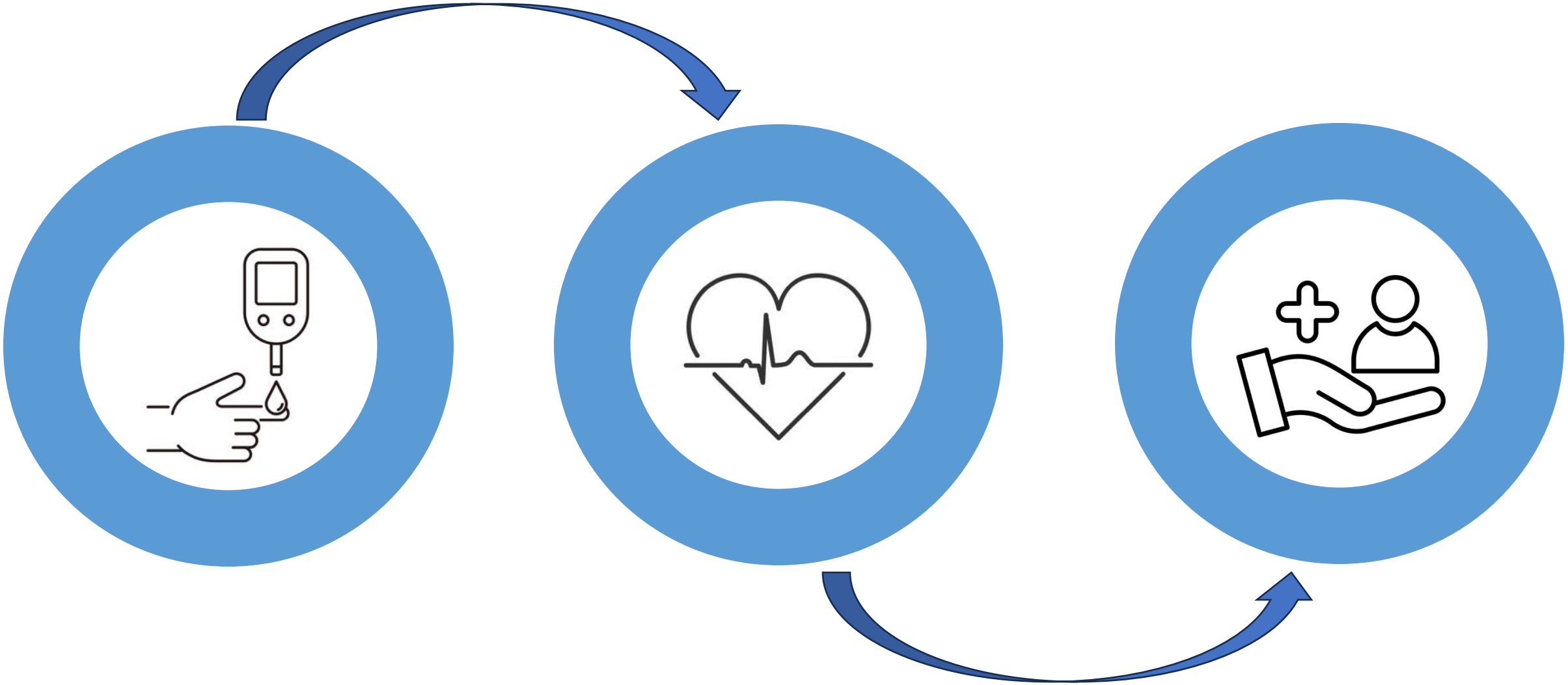


Kessler JA et al, Clin Transl Sci 2021; 14: 1176-1184

Take home messages

- **Obiettivi terapie del futuro: miglior controllo glicemico e riduzione significativa del peso, come da indicazione ADA ed EASD;**
- **Uso di Disease Modifying Drugs può cambiare prevalenza futura di diabete;**
- **Approcci terapeutici futuri per migliorare la compliance dei pazienti;**
- **Novità nell'ambito delle complicanze = collaborazione diabetologica con sempre più specialisti.**

Il cambio di paradigma della Diabetologia



Il futuro è patient-centred