EndoDia Centre

Endokrinologie- und Diabetologie-Zentrum
Centre d'endocrinologie – diabétologie

New kids on the block

Post-ADA 31.08.2023

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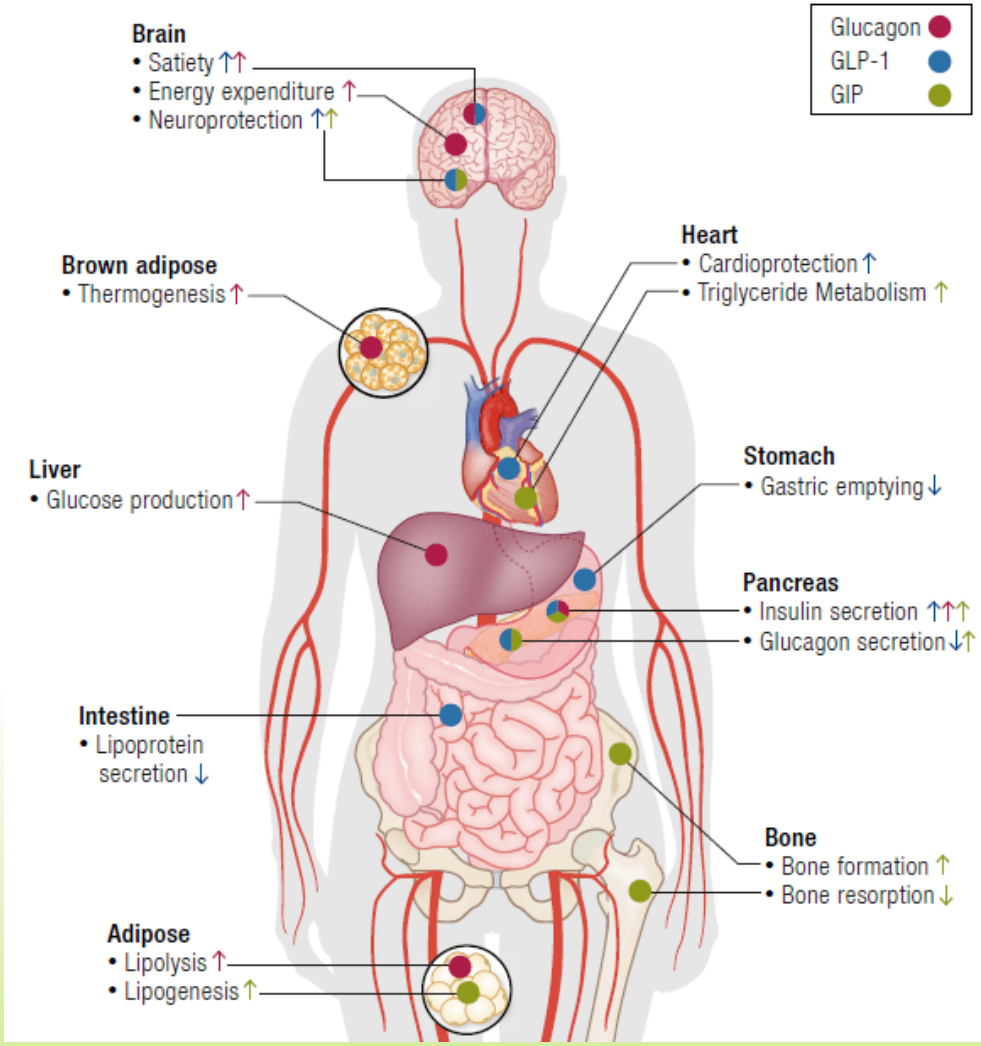
EndoDia Centre, Biel/ Bienne

New kids on the block

- Incretins and beyond for treatment of T2D and overweight/obesity
  - **Background**
  - Triagonist: Retatrutide
  - Dual agonist: Tirzepatide
  - Single agonists: Semaglutide, Orforglipron
- Weekly insulin: Icodec
- Prevention trials in Type 1 Diabetes

Incretins & glucagon: Background

- GLP-1, GIP and Glucagon exert their effects through similar mechanisms of action, all acting on G protein-coupled receptors (GPCRs) and mediating signal transduction through cAMP stimulation
- Tissue-specific distribution of the incretin/ glucagon receptors is unique, supporting their combined use to treat diabetes and obesity



M. Capozzi et al, Endocrine Reviews, Oct 2018, 39(5): 719-38

Incretins & glucagon: Background

- **GIP (Glucose-dependent Insulinotropic Peptide)** is a 42-aminoacid peptide secreted by K-cells in the intestine in response to nutrients
- GIP stimulates insulin in a glucose-dependent manner
- Beneficial effect particularly when coupled with GLP-1R agonism (synergism)

- **Glucagon** is a 29-aminoacid peptide hormone produced by pancreatic alpha-cells
- Hyperglycemic effect mediated through stimulation of glycogenolysis and gluconeogenesis in the liver
- Insulinotropic activity
- Brain glucagon receptor activation stimulates satiety and energy expenditure

- **Triagonism:**
  - GLP-1 agonists→ weight loss & insulin secretion
  - GIPR agonism → buffers glucagon-mediated hepatic glucose secretion via amplification of insulin secretion; superior benefits of dual GIP-/ GLP1 receptor agonists in the CNS (satiety and weight loss)
  - GCGR agonism→ independent complimentary weight loss

M. Capozzi et al, Endocrine Reviews, Oct 2018, 39(5): 719-38

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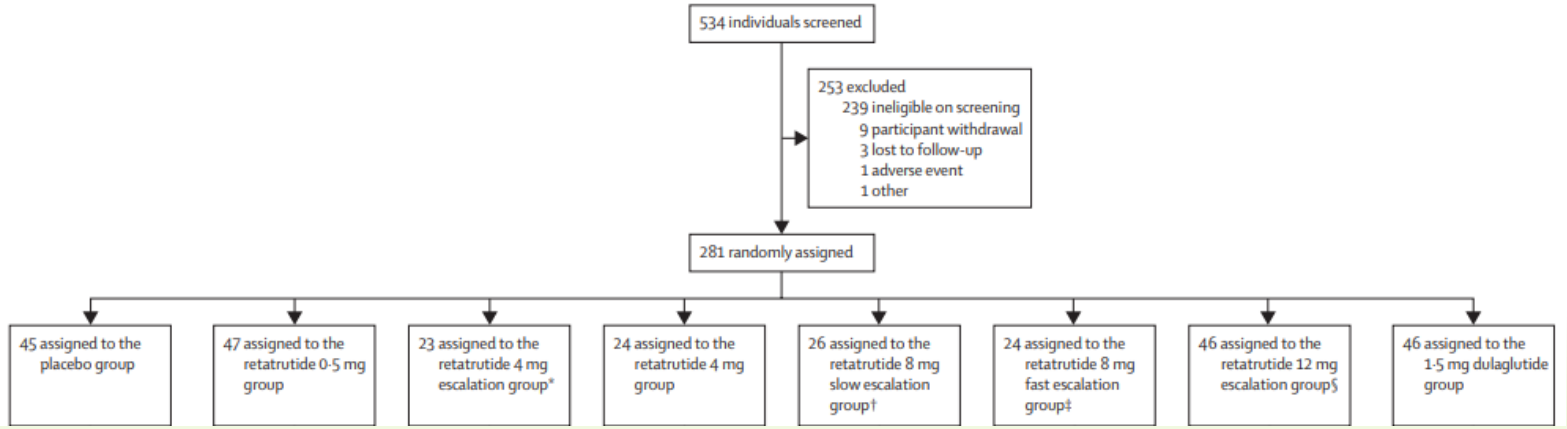
Retatrutide in Type 2 Diabetes

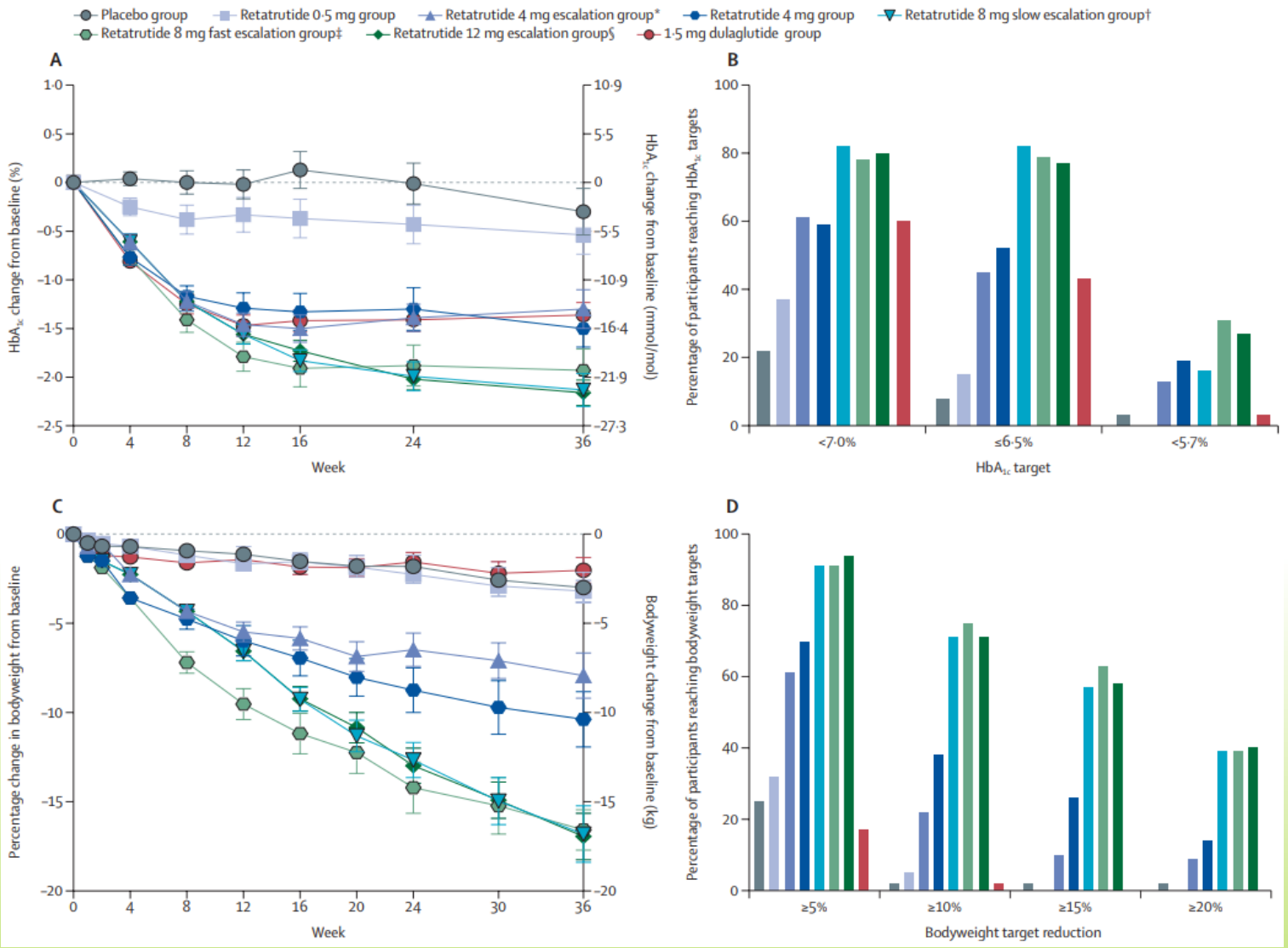
- Randomised, double-blind, placebo and active-controlled, parallel-group phase 2 trial conducted in the USA
- Once-weekly injections of placebo/ 1.5 mg dulaglutide/ retatrutide 0.5 – 12 mg



- Primary endpoint: change in HbA1c from baseline to 24w
- Secondary endpoints: change in HbA1c and BW at 36 w, % of patients reaching HbA1c< 7% at 24 and 36 weeks

J.Rosenstock, The Lancet, 2023 (402):529-544

Retatrutide T2D: results



- HbA1c reduction up to -2.02% at 24 weeks and -2.16% at 36 weeks
- BW reduction up to 16.94% at 36 weeks

J.Rosenstock, The Lancet, 2023 (402):529-544

Retatrutide T2D: safety

- AE mainly gastrointestinal (dose-dependent): nausea, diarrhoea, vomiting, constipation (up to 50% with retatrutide vs 13% placebo vs 35% dulaglutide)
- Overall, 8% discontinued the study due to AE
- Severe AE: 1 cholecystitis, 1 acute pancreatitis, 1 starvation ketoacidosis
- Moderate hypoglycemia in 3 retatrutide patients, no severe hypoglycemia

J.Rosenstock, The Lancet, 2023 (402):529-544

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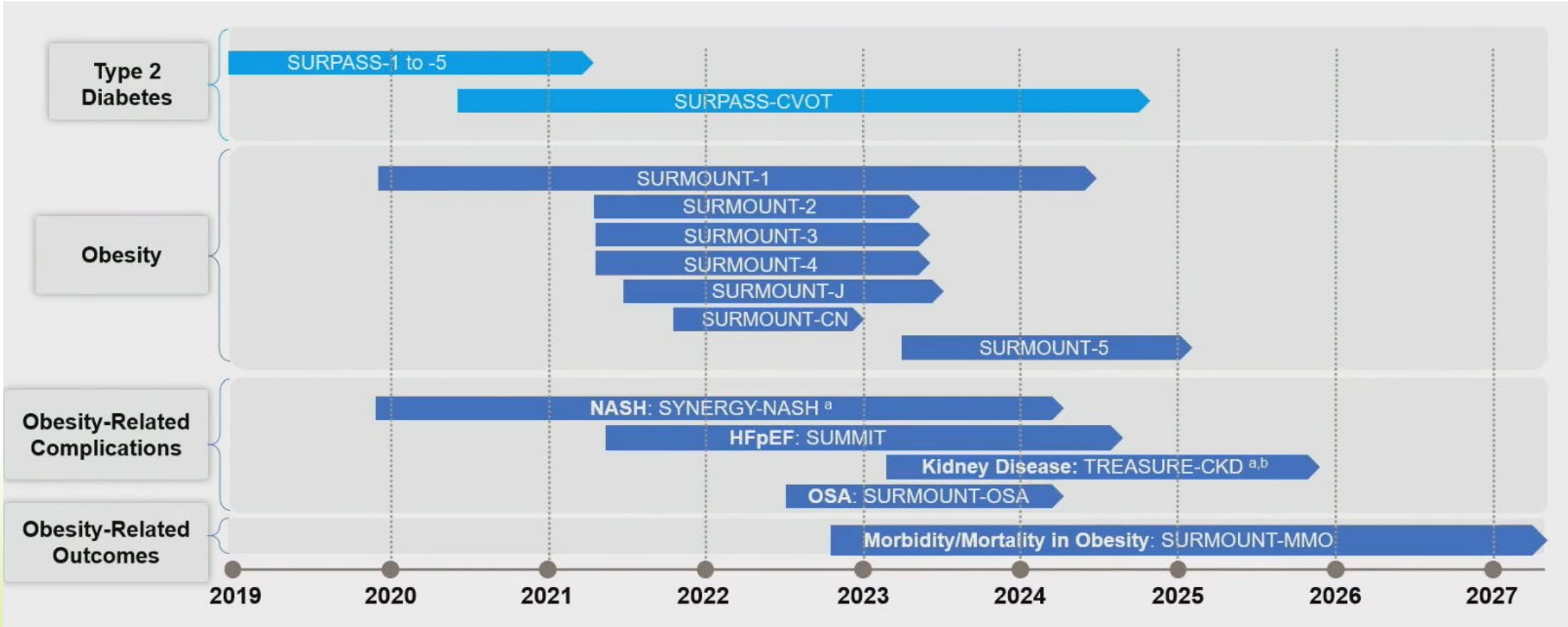
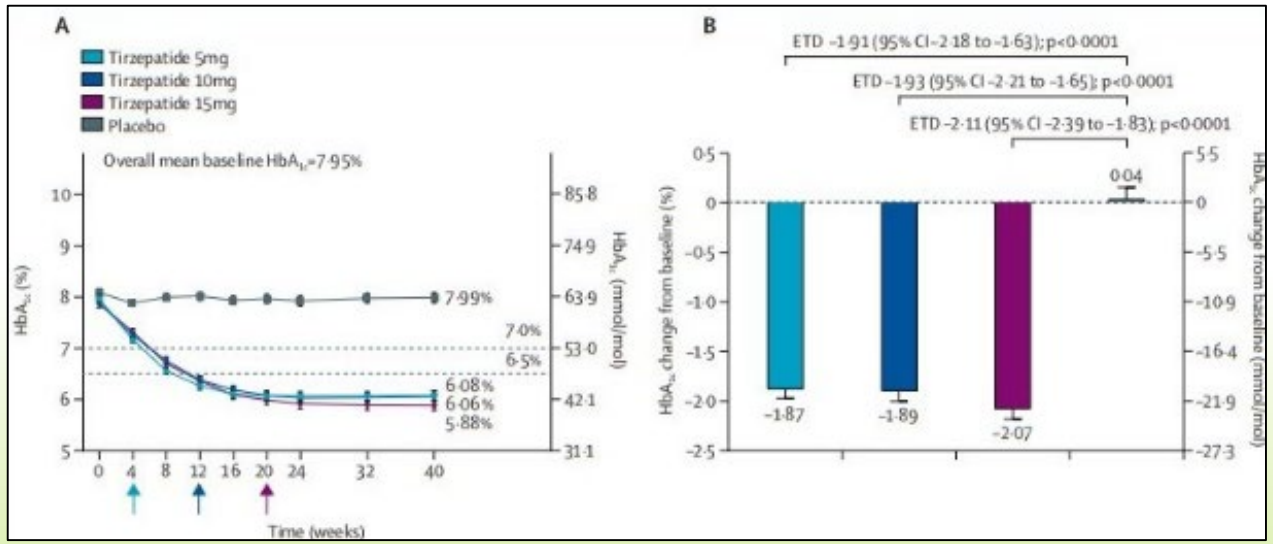
Tirzepatide studies



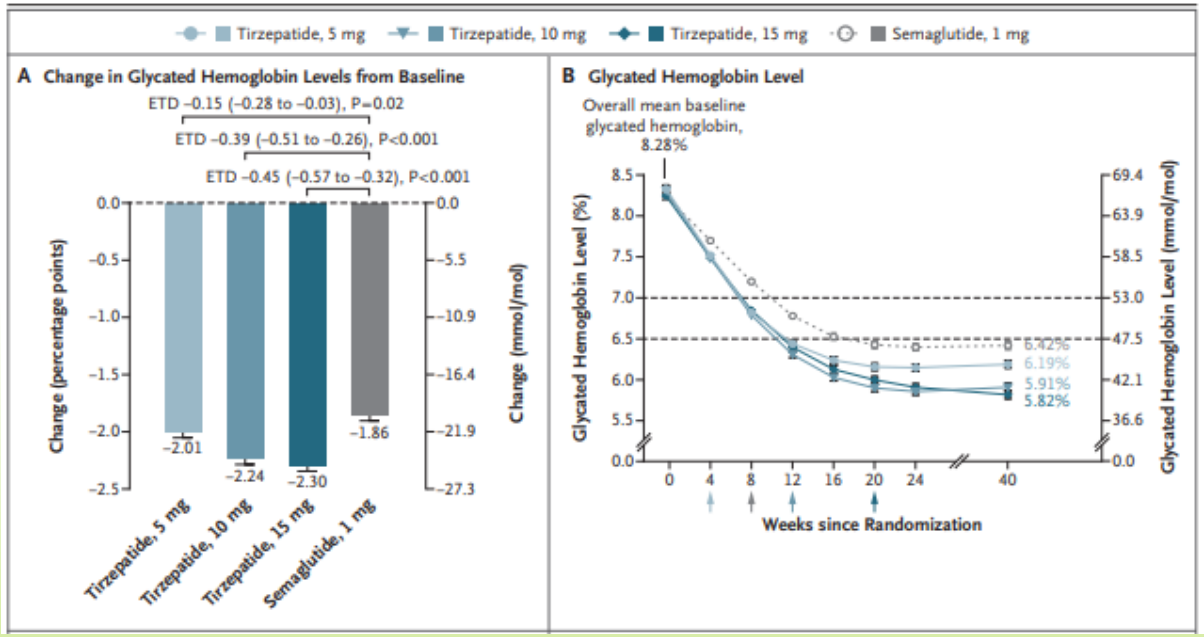
J.Frias, ADA sessions 2023

Tirzepatide in T2D: SURPASS

SURPASS-1 (Tirzepatide 5, 10 or 15 mg weekly vs Placebo)



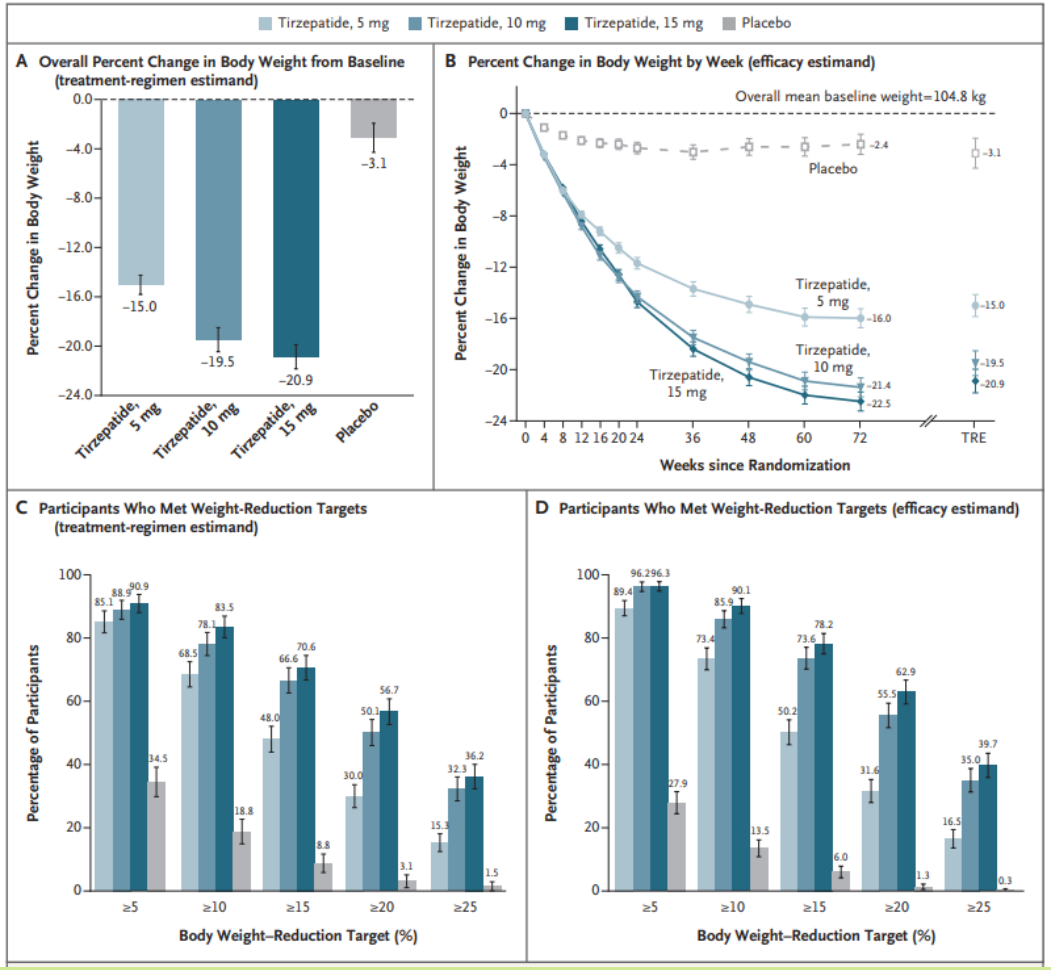
SURPASS-2 (Tirzepatide 5, 10 or 15 mg weekly vs semaglutide 1mg weekly)



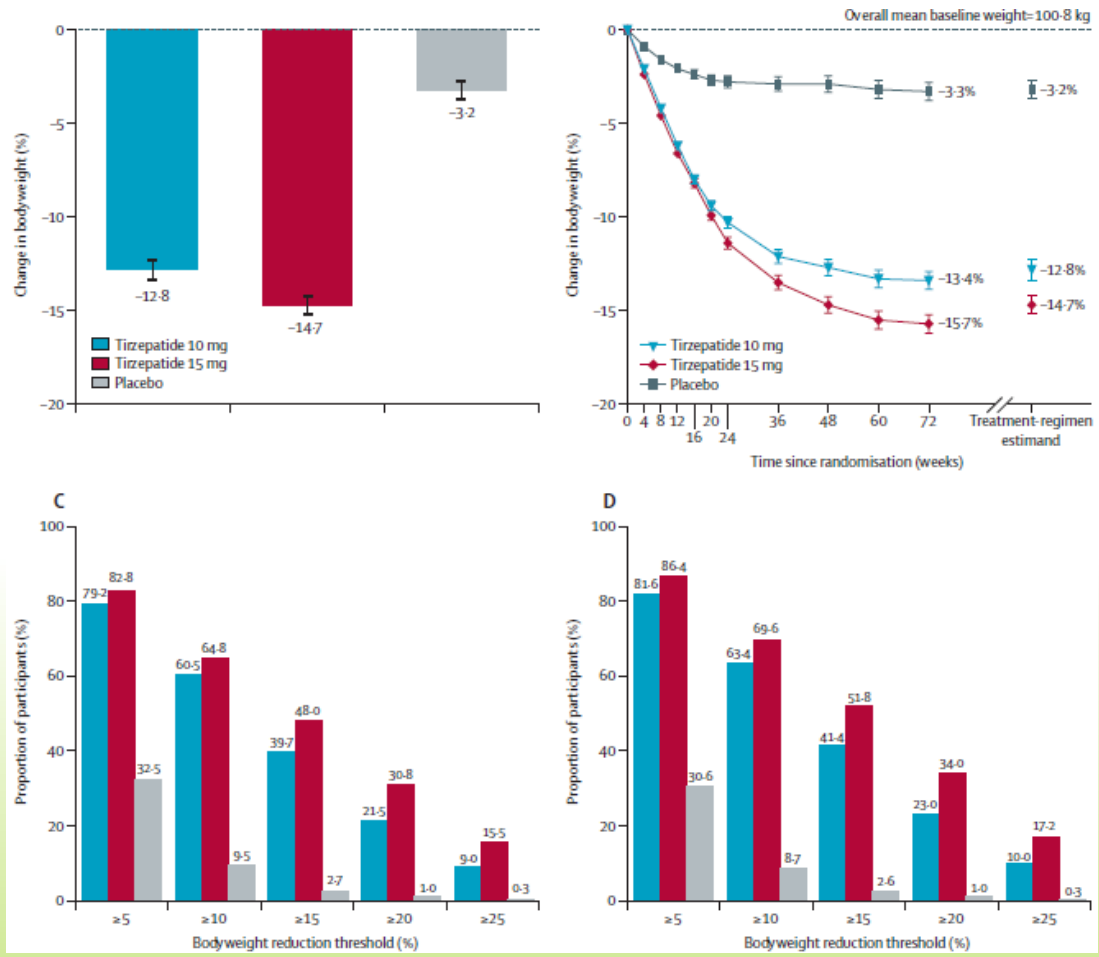
J.Rosenstock et al, The Lancet 2021;398:143-155
J.Frias et al, NEJM 2021;385:503-15

Tirzepatide in obesity: SURMOUNT 2

SURMOUNT-1: Tirzepatide 5, 10 or 15 mg weekly vs placebo in obese patients



SURMOUNT-2: Tirzepatide 10 or 15 mg weekly vs placebo in patients with T2D and obesity



A.Jastreboff et al, N Engl J Med 2022;387:205-16
T.Garvey et al, The Lancet, June 26, 2023

Tirzepatide: SURMOUNT 2

Secondary endpoint

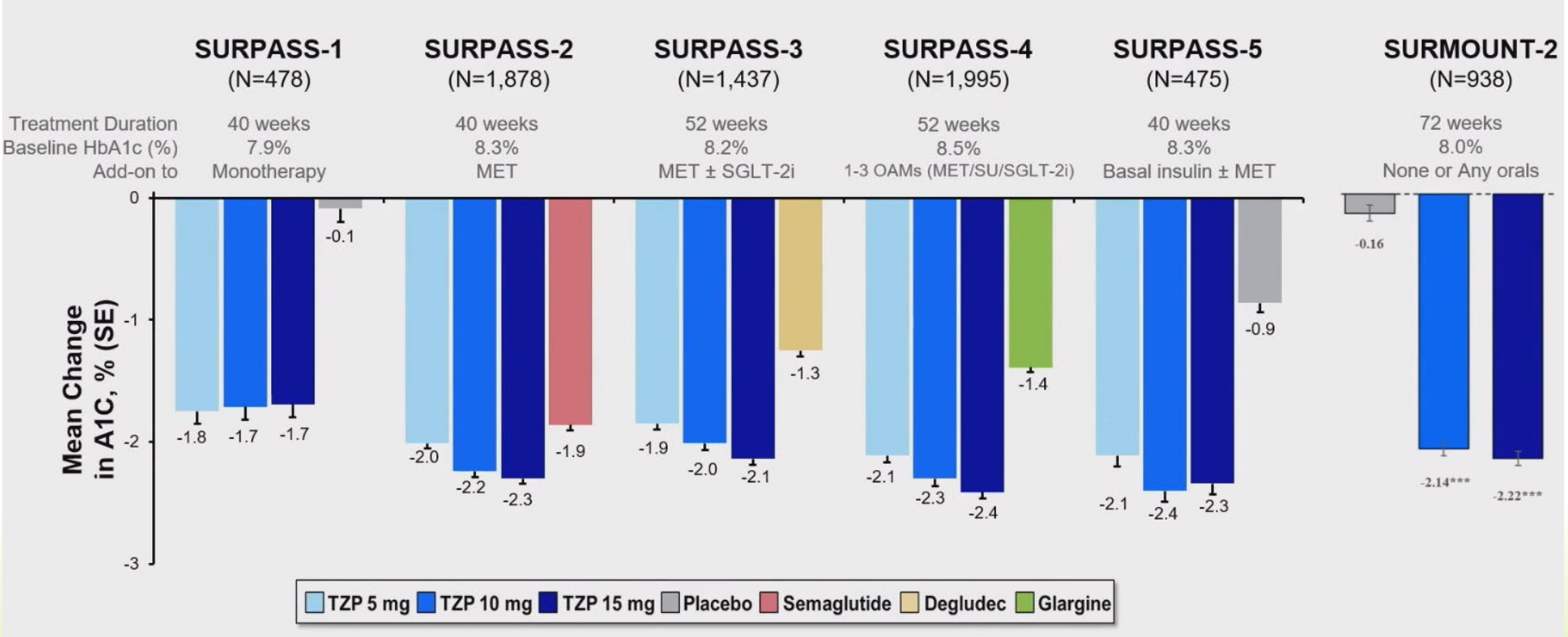
- HbA1c: -2,1% with Tirzepatide
- > 80% achieved recommended target < 7%
- > 75% achieved A1c< 6,5%
- > 45% achieved normoglycemia

Safety/ tolerability

- AE mostly gastrointestinal, occurred primarily during dose-escalation, were mild-to-moderate and decreased over time
- Level 2 hypoglycemia rare
- Increase in mean levels pancreatic enzymes (in normal range), 3 acute pancreatitis (2 with T 15 mg, 1 placebo)

T.Garvey et al, The Lancet, June 26, 2023

SURMOUNT 2 vs SURPASS trial results

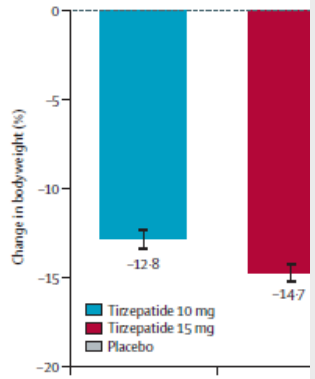


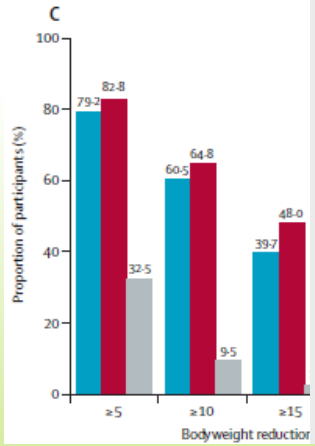
Similar HbA1c reduction, occurred earlier (at 12w) in SURMOUNT-2
Weight loss: -11.4% / -13.9% in SURPASS 3, -13.4%/ -15.7% in SURMOUNT-2

I.Lingvay, ADA 2023 sessions

SURMOUNT 2 VS STEP 2 results

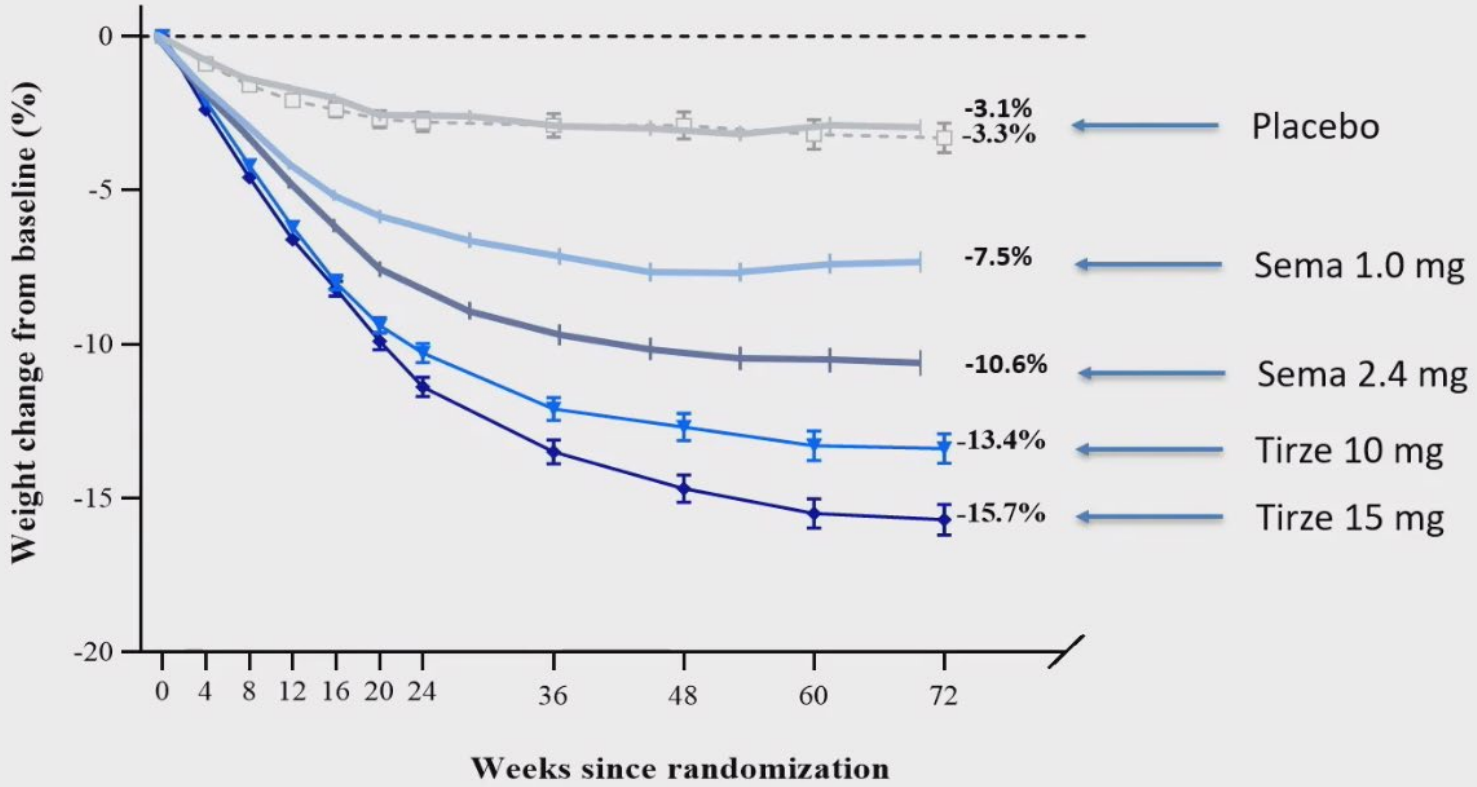
SURMOUNT 2: Tirzepa **o in patients and obesity**

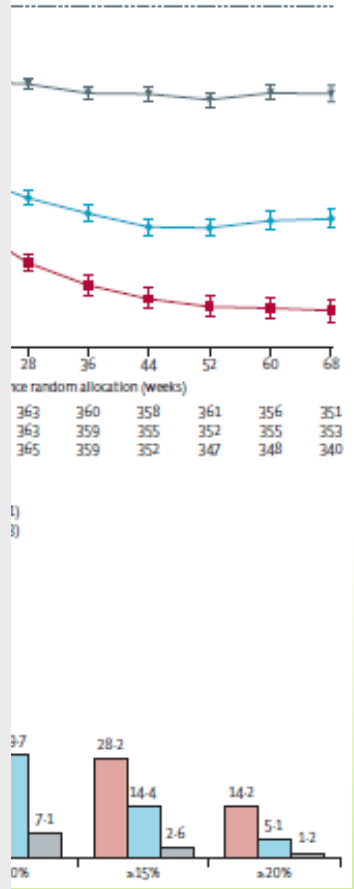




SURMOUNT 2 vs STEP 2: Change in body weight

Baseline weight 100.8 kg in SURMOUNT 2 and 99.8 kg in STEP 2





T.Garvey et al, The Lancet, June 26, 202
M.Davies et al, The Lancet, 2021(397):971-98
I.Lingvay, ADA 2023 session

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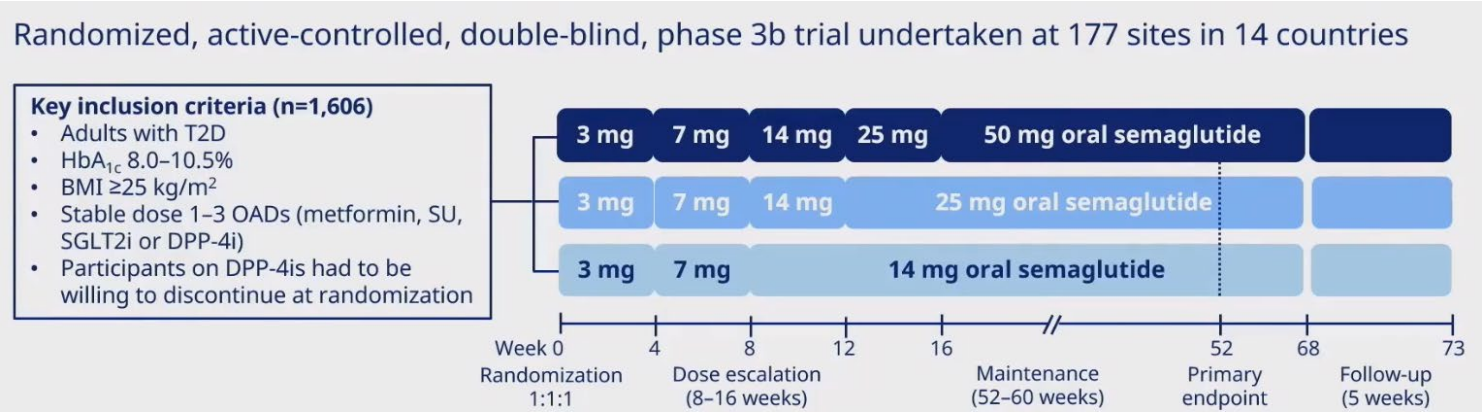
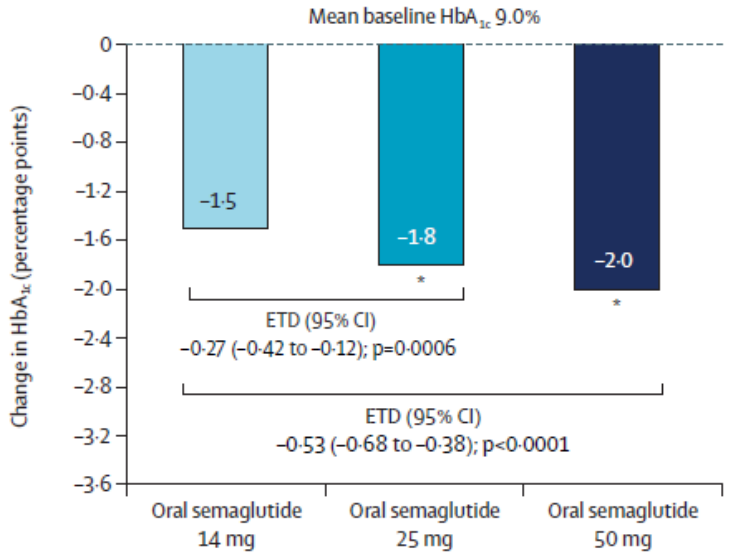
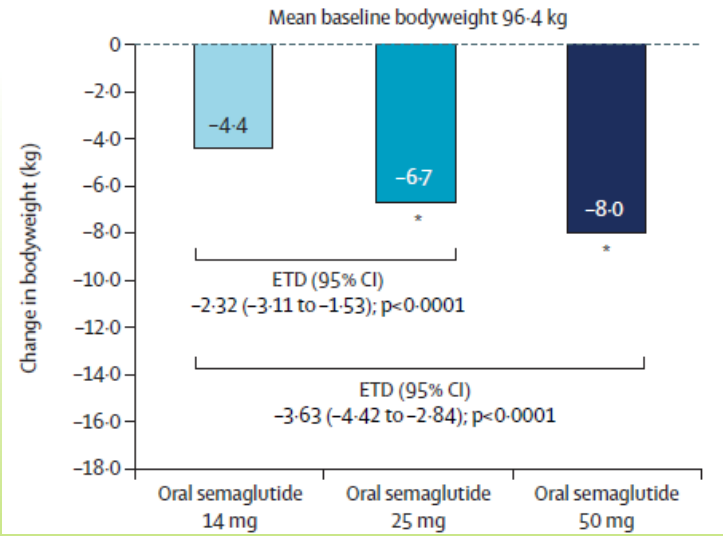
Oral Semaglutide for Treatment of Type 2 Diabetes and Obesity

- PIONEER PLUS: to evaluate the efficacy, safety and tolerability of once-daily oral semaglutide 25 and 50 mg compared to 14 mg in adults with T2DM
- OASIS 1: to evaluate the efficacy and safety of once-daily oral semaglutide 50 mg plus lifestyle in people with overweight/ obesity
- New formulation of oral semaglutide, with higher bioavailability

PIONEER PLUS: semaglutide 25 and 50 mg compared to 14 mg in adults with T2D





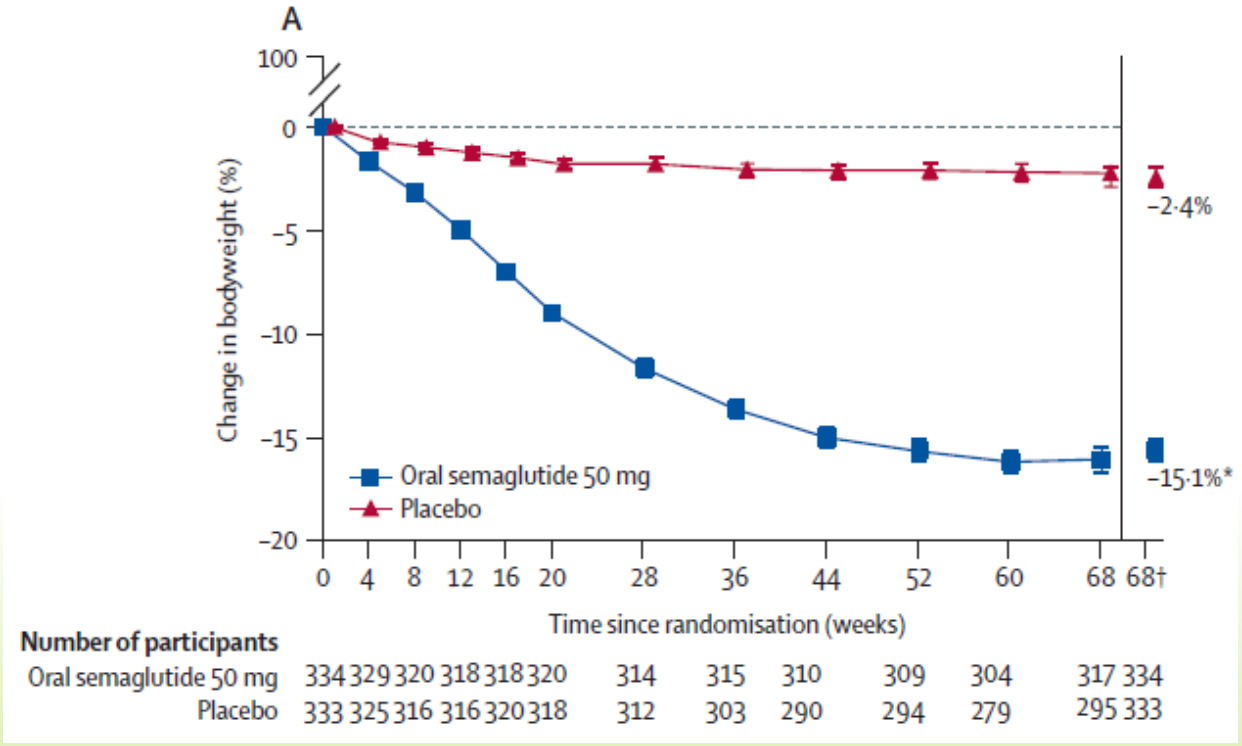


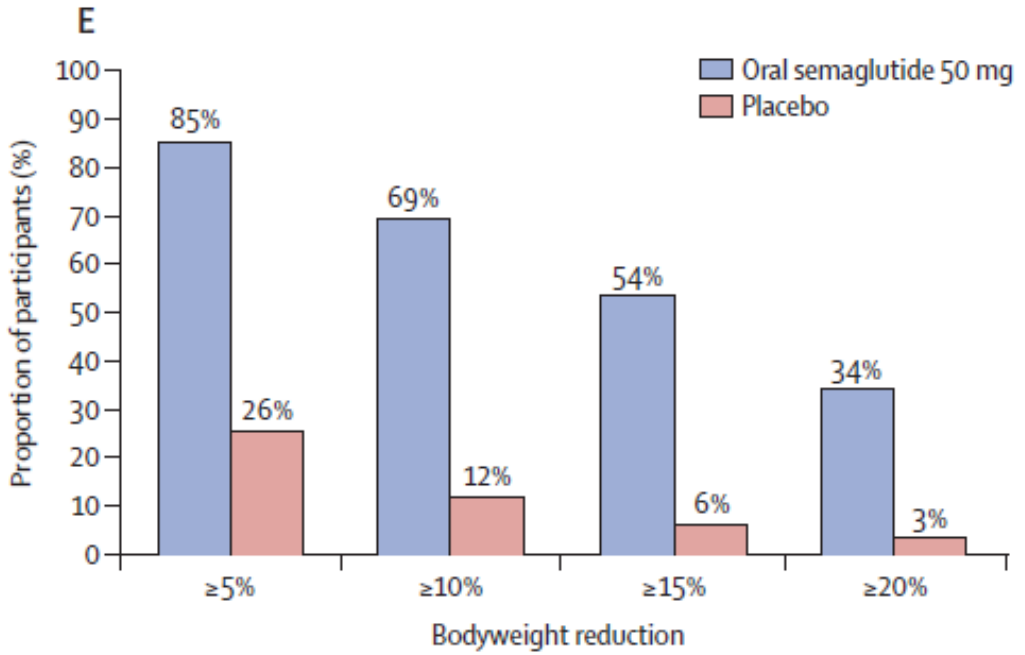
Conclusion: superior glycemic control and weight loss compared to 14 mg dose

AEs: Nausea (18-27%), vomiting (10-18%)

S. Pedersen, ADA sessions 2023
T.Garvey et al, The Lancet, June 26, 2023

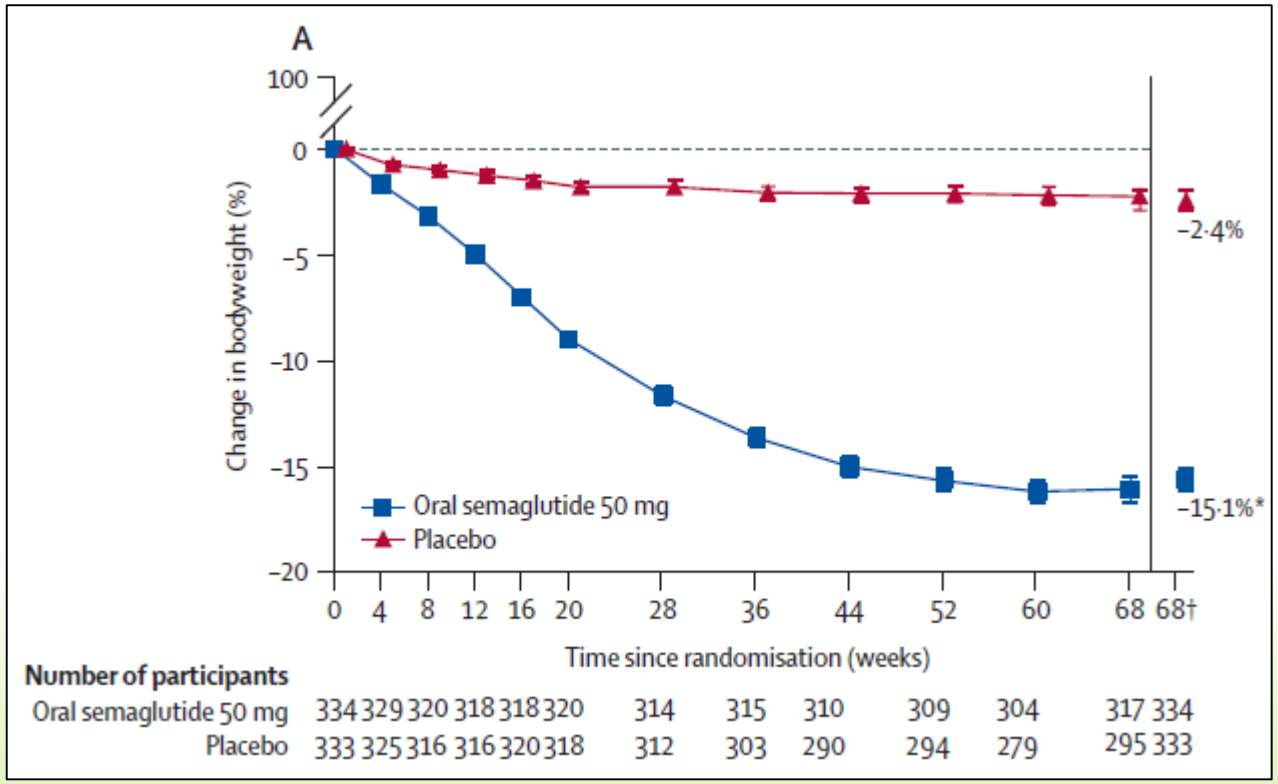
OASIS 1: Once-daily semaglutide 50 mg vs Placebo in obesity

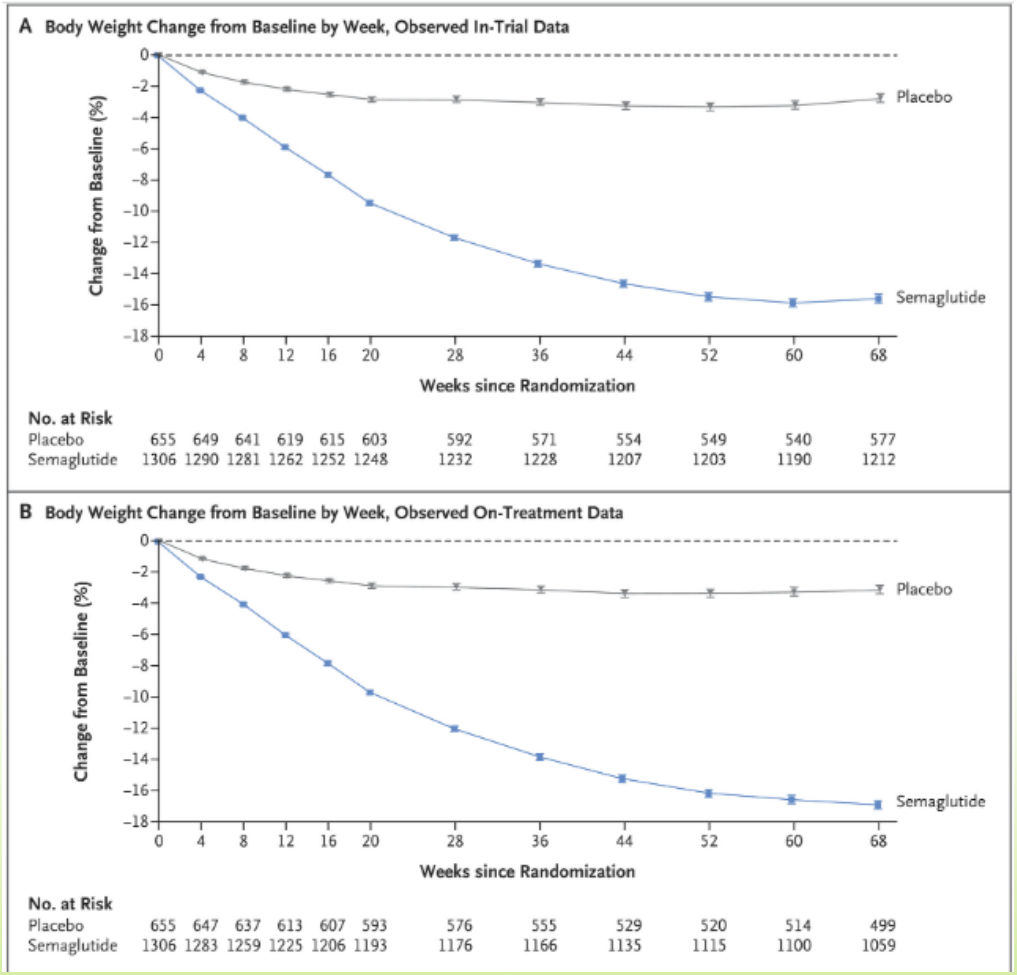




F.Knop et al, Lancet, June 26, 2023

OASIS 1 vs STEP 1 results





Similar weight loss achieved with Semaglutide 50 mg daily oral and 2,4 mg weekly s.c.

F.Knop, Lancet, June 26, 2023
STEP1 Trial, N Engl J Med 2021;384:989-1002

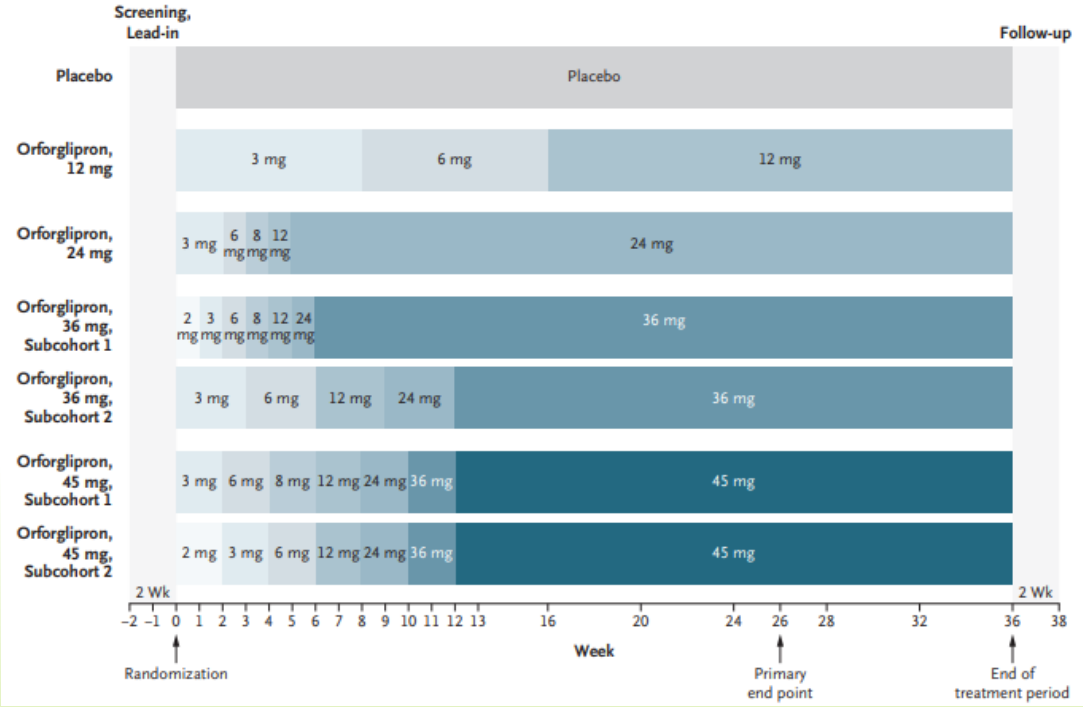
OASIS 1: Once-daily semaglutide 50 mg in obesity

- Adverse events: 91,9% Semaglutide 50 mg vs 85,6% placebo
- Leading to discontinuation: 5,7 vs 3,6%
- Nausea 51,8 vs 15,3%
- Vomiting 24,6 vs 3,6%
- Diarrhea 26,6% vs 16,8%
- Altered skin sensation 13 vs 1%

F.Knop et al, Lancet, June 26, 2023

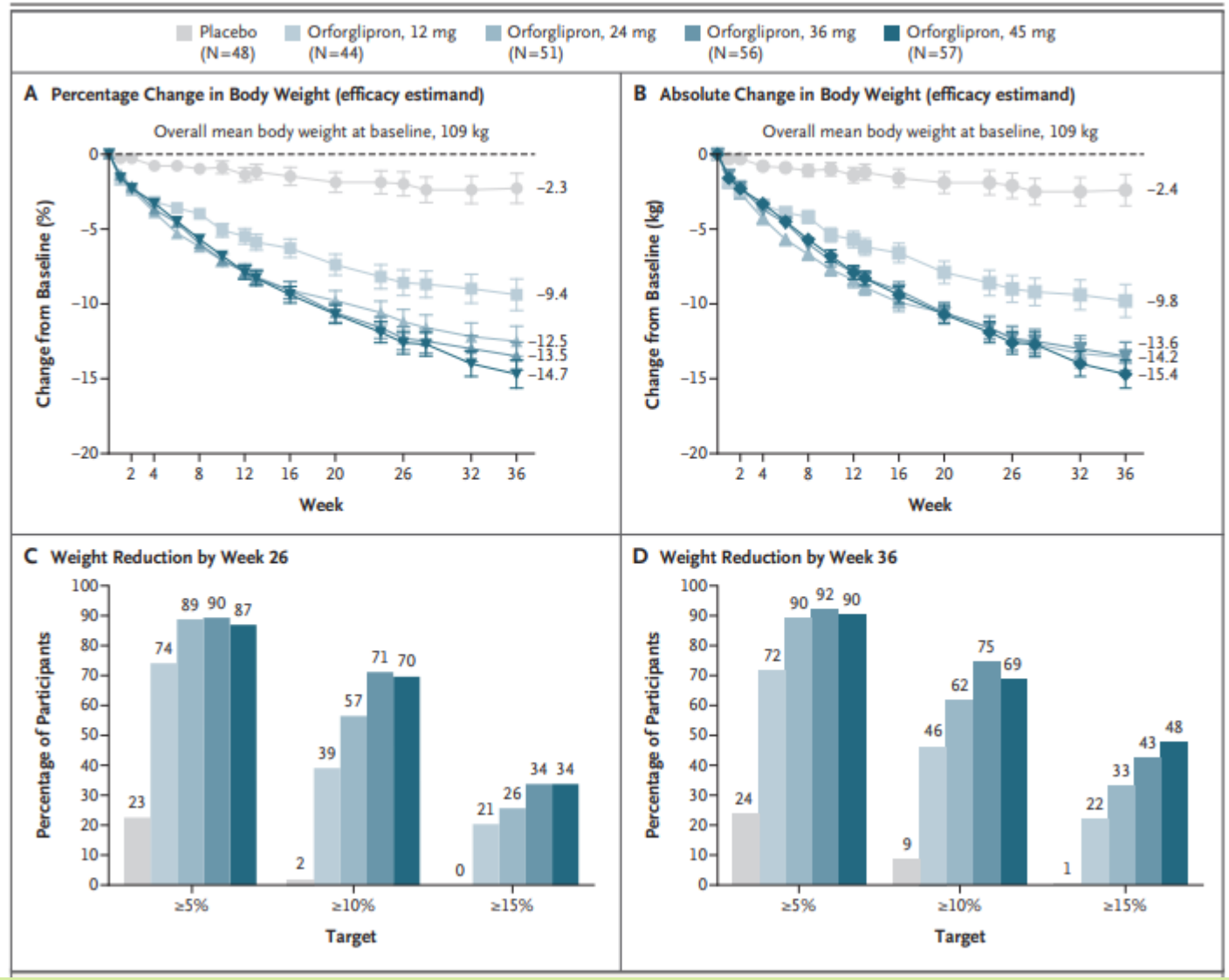
Effect of oral non-peptide GLP-1 R agonist Orforglipron in participants with overweight/ obesity: A phase 2 study

- Novel, once daily, non-peptide GLP-1 receptor agonist
- In development as an oral treatment for obesity and T2D in adults
- Oral bioavailability 30-40%
- No restriction of food, water or other medications
- **Study objective:** to evaluate efficacy and safety of orforglipron compared with placebo for weight management



S.Wharton et al, NEJM, June 23, 2023

Effect of oral non-peptide GLP-1 R agonist Orforglipron in participants with overweight/ obesity: Results



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ONWARDS 3: icodec vs degludec

- Icodec is a once-weekly basal insulin analog in development
- Albumin binding, combined with reduced insulin-receptor affinity, ensures slow clearance and the formation of an inactive albumin-bound depot
- Gradual, continous release of icodec from the depot leads to prolonged action with a half-life of appr. 1 week

- ONWARDS 3 objective: to assess the efficacy and safety of once-weekly icodec vs once-daily degludec in people with insulin-naïve T2D inadequately controlled by non-insulin glucose-lowering agents

Nishimura et al, BMJ Open Diab Res Care 2021;9:e002301
Philis-Tsimikas et al, Diabetes Obes Metab 2023(25):331-341

ONWARDS trials on Icodec

	T2D: Insulin-naive			T2D: Previously insulin-treated		T1D
	ONWARDS 1	ONWARDS 3	ONWARDS 5	ONWARDS 2	ONWARDS 4	ONWARDS 6
	NCT04460885[a]	NCT04795531[b]	NCT04760626[c]	NCT04770532[d]	NCT04880850[e]	NCT04848480[f]
Key trial details						
Trial design	Randomized open label	Randomized double-blind	Randomized open label real-world elements	Randomized open label	Randomized open label	Randomized open label
Estimated sample size required, N	970	580	1096	520	580	580
Study start date	November 2020	March 2021	March 2021	March 2021	May 2021	April 2021
Trial duration	78 wk (52-wk main phase +26-wk extension phase) + 5-wk follow-up period	26 wk + 5-wk follow-up period	52 wk + 5-wk follow-up period	26 wk + 5-wk follow-up period	26 wk + 5-wk follow-up period	52 wk (26-wk main phase + 26-wk extension phase) + 5-wk follow-up period
Interventions						
Icodec arm	Once-weekly icodec + non-insulin glucose-lowering agents	Once-weekly icodec + non-insulin glucose-lowering agents + once-daily placebo	Once-weekly icodec (with digital titration solution) ± non-insulin glucose-lowering agents	Once-weekly icodec ± non-insulin glucose-lowering agents	Once-weekly icodec ± non-insulin glucose-lowering agents + aspart 2-4 times daily	Once-weekly icodec + aspart ≥2 times daily
Comparator arm	Once-daily glargine U100 + non-insulin glucose-lowering agents	Once-daily degludec + non-insulin glucose-lowering agents + once-weekly placebo	Once-daily basal insulin analogues (degludec, glargine U100 or U300) + non-insulin glucose-lowering agents	Once-daily degludec ± non-insulin glucose-lowering agents	Once-daily glargine U100 ± non-insulin glucose-lowering agents + aspart 2–4 times daily	Once-daily degludec + aspart ≥2 times daily
Key inclusion criteria						
Diagnosis	T2D diagnosed ≥180 d prior to screening					T1D diagnosed ≥1 y prior to screening
Demographics	Male or female age ≥ 18 y at the time of signing informed consent					
Screening HbA_{1c}	7.0%-11% (53.0-96.7 mmol/mol)		>7.0% (53 mmol/mol)	7.0%-10.0% (53.0-85.8 mmol/mol)		<10% (85.8 mmol/mol)
BMI, kg/m^2	≤40.0		N/A	≤40.0		N/A
Prior insulin treatment	Insulin-naive Short-term insulin treatment periods for a maximum of 14 d prior to the day of screening or prior insulin treatment for gestational diabetes are permitted			Insulin treatment ≥90 d prior to the day of screening Once-daily or twice-daily basal insulin: NPH insulin, degludec, detemir, glargine U100 or U300	Insulin treatment ≥90 d prior to the day of screening Daily basal insulin: NPH insulin, degludec, detemir, glargine U100 or U300 Bolus insulin analogue: aspart, faster aspart, lispro, faster lispro or glulisine 2-4 times daily	MDI ≥1 y prior to the day of screening

Philis-Tsimikas et al, Diabetes Obes Metab 2023(25):331-341

ONWARDS 3: icodec vs degludec

- Primary endpoint: Change in A1c from baseline to week 26
- Secondary endpoints: clinical significant (level 2) and severe (level 3) hypoglycemia, mean insulin weekly dose and BW change
- Titration algorithm:
  - starting dosage 70 U/week (icodec) or 10 U/day (degludec)
  - Pre-breakfast SMBG target: 4,4 – 7,2 mmol/L
  - If mean SMBG above goal: dose increased + 20U/week resp. + 3U/day
  - If mean SMBG below goal: dose decreased - 20U/week resp. - 3U/day

Lingway et al, JAMA 2023;330(3):228-238

ONWARDS 3: icodec vs degludec

Characteristic	No. (%) Once-weekly insulin icodec (n = 294)	Once-daily insulin degludec (n = 294)
Men	185 (62.9)	184 (62.6)
Women	109 (37.1)	110 (37.4)
Age, mean (SD), y[a]	58 (10)	59 (10)
Diabetes duration, median (IQR), y	10.5 (5.8-14.7)	10.7 (6.3-16.1)
Race[b]		
American Indian or Alaska Native	0	1 (0.9)
Asian	80 (27.2)	85 (28.9)
Black or African American	9 (3.1)	6 (2.0)
White	179 (60.9)	175 (59.5)
Other[c]	11 (3.7)	11 (3.7)
Not reported[d]	15 (5.1)	16 (5.4)
Ethnicity		
Hispanic or Latino	76 (25.9)	88 (29.9)
Not Hispanic or Latino	203 (69.0)	190 (64.6)
Not reported[d]	15 (5.1)	16 (5.4)
Body weight, mean (SD), kg[a]	85.8 (20.1)	83.2 (18.2)
Body mass index, mean (SD)[a]	29.9 (5.2)	29.2 (5.1)
HbA_{1c}, mean (SD), %[a]	8.55 (1.11)	8.48 (1.01)
Concomitant noninsulin glucose-lowering agent use at baseline		
Metformin	266 (90.5)	264 (89.8)
Sulfonylureas	132 (44.9)	128 (43.5)
Sodium-glucose cotransporter 2 inhibitor	119 (40.5)	95 (32.3)
Dipeptidyl peptidase 4 inhibitor	76 (25.9)	80 (27.2)
Glucagon-like peptide 1 receptor agonists	64 (21.8)	48 (16.3)
Thiazolidinediones	26 (8.8)	19 (6.5)
α-Glucosidase inhibitor	18 (6.1)	20 (6.8)
Glinides	7 (2.4)	4 (1.4)
No. of noninsulin glucose-lowering agents used at baseline		
1	69 (23.5)	84 (28.6)
2	130 (44.2)	121 (41.2)
≥3	94 (32.0)	88 (29.9)
Comorbidities of interest present in ≥5% of participants[e]		
Hypertension	199 (67.7)	181 (61.6)
Coronary artery disease	30 (10.2)	29 (9.9)
Diabetic nephropathy	30 (10.2)	19 (6.5)
Hepatic steatosis	28 (9.5)	45 (15.3)
Peripheral venous disease	15 (5.1)	14 (4.8)

Lingway et al, JAMA 2023;330(3):228-238

ONWARDS 3: icodec vs degludec

Outcome	Once-weekly icodec (n = 294)			Once-daily degludec (n = 294)			Estimated treatment difference in icodec vs degludec (95% CI)	*P* value[a]
	Baseline	Week 26	Change from baseline to week 26	Baseline	Week 26	Change from baseline to week 26		
Primary end point								
HbA_{1c}, %	8.6	7.0	−1.6 percentage points	8.5	7.2	−1.4 percentage points	−0.2 (−0.3 to −0.1) percentage points	<.001[b]; .002[c]
Key secondary end points								
Fasting plasma glucose, mg/dL	187	127	−54	176	127	−54	0 (−6 to 5)	.90
Mean insulin dose from week 24 to 26, U/week	69	204		70	186		Estimated treatment ratio, 1.10 (0.98 to 1.22)	.09
Mean body weight, kg	85.8	87.3	2.8	83.2	86.8	2.3	0.46 (−0.19 to 1.10)	.17

- 56,8% vs 41,6% reached target A1c< 7%
- 52,2% vs 39,9% reached target A1c< 7% without level 2 or 3 hypogylcemia during the prior 12 weeks
- Daily insulin dose over time: 0,34 vs 0,31 U/kg/day
- No severe hypoglycemia
- 8% of patients on icodec experienced level 2 hypoglycemia

Lingway et al, JAMA 2023;330(3):228-238

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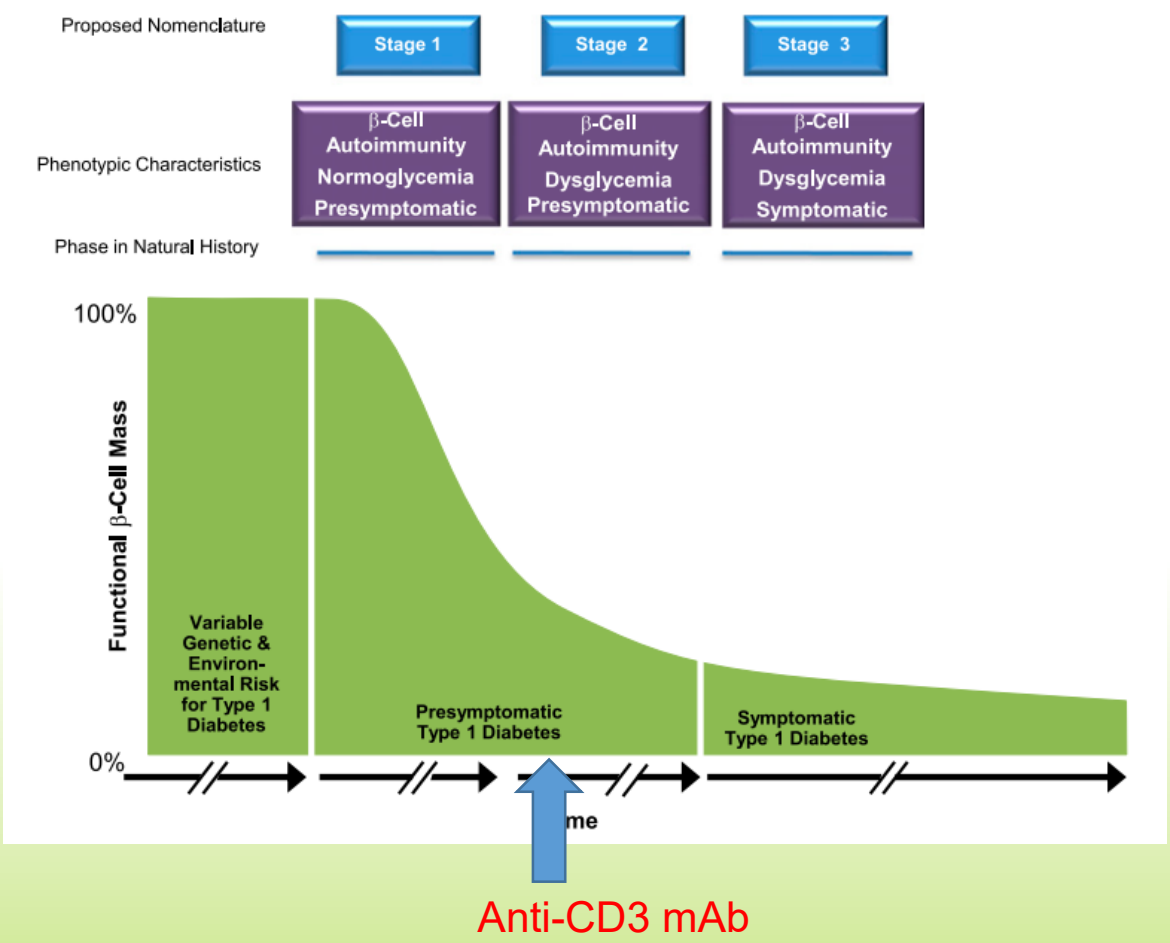
Prevention trials of T1D



- **Stage 1:** ≥ 2 Autoantibodies to insulin, GAD65, IA-2 and/ or ZnT8
- **Stage 2:** autoantibodies AND dysgylcemia (impaired fasting glucose, impaired glucose tolerance and/ or A1c ≥ 5,7%
- **Stage 3:** symptomatic T1D
- **Stage 4:** long-standing T1D

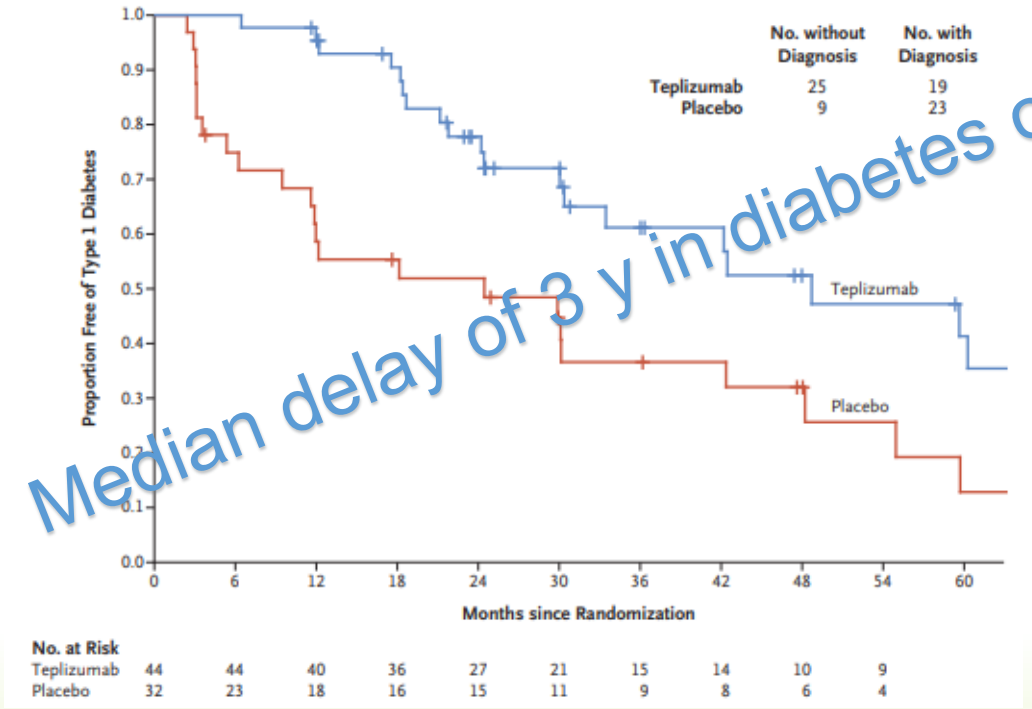
Insel et al, Diabetes Care 2015;38:1964-74

An Anti-CD3 Antibody, Teplizumab, in Relatives at risk for T1D

Type 1 Diabetes TrialNet

Table 1. Baseline Characteristics of the Participants.*

Characteristic	Teplizumab (N=44)	Placebo (N=32)
Age — yr		
Median (IQR)	14 (12–22)	13 (11–16)
Range	8.5–49.5	8.6–45.0
Age <18 yr — no. (%)	29 (66)	26 (81)
Male sex — %	57	53
Relationship to person with type 1 diabetes — no. (%)		
Sibling†	28 (64)	16 (50)
Offspring	6 (14)	6 (19)
Parent	6 (14)	3 (9)
Sibling and another first-degree relative	2 (5)	3 (9)
Second-degree relative	2 (5)	3 (9)
Third-degree relative or further removed	0	1 (3)
Autoantibodies — no. of participants positive (%)‡		
Anti-GAD65, harmonized	40 (91)	28 (88)
Micro insulin	20 (45)	11 (34)
Anti–IA-2, harmonized	27 (61)	24 (75)
ICA	29 (66)	28 (88)
Anti-ZnT8	32 (73)	24 (75)
Median glycated hemoglobin level (IQR) — %	5.2 (4.9–5.4)	5.3 (5.1–5.4)

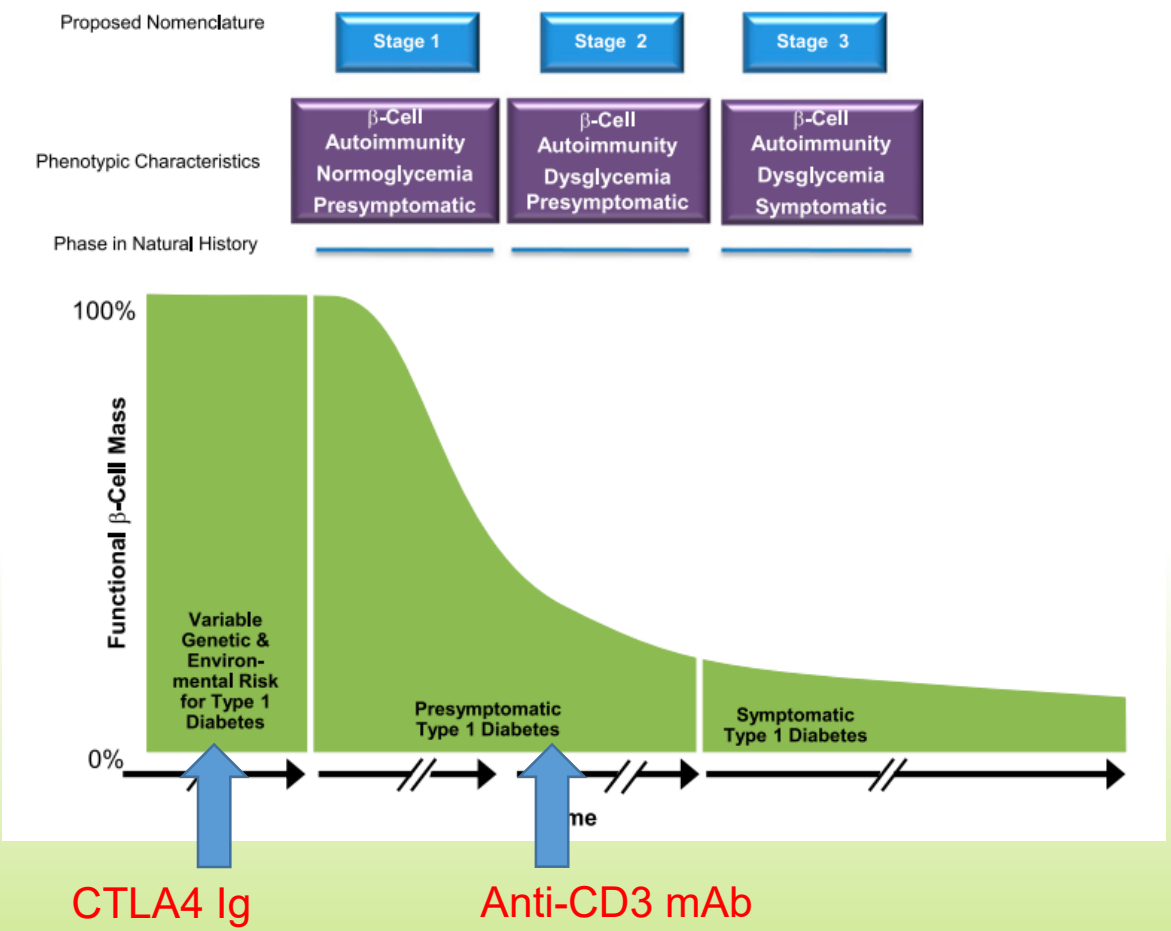


Median delay of 3 y in diabetes onset

- 2-arm, multicenter, randomized, double-masked, placebo-controlled trial in high-risk AB-positive non-diabetic relatives of patients with T1D (stage 2)
- 14 day outpatient infusion of Teplizumab vs placebo
- Primary outcome: comparison of time to diagnosis T1D

Herold et al, N Engl J Med 2019;381:603-13

Prevention trials of T1D



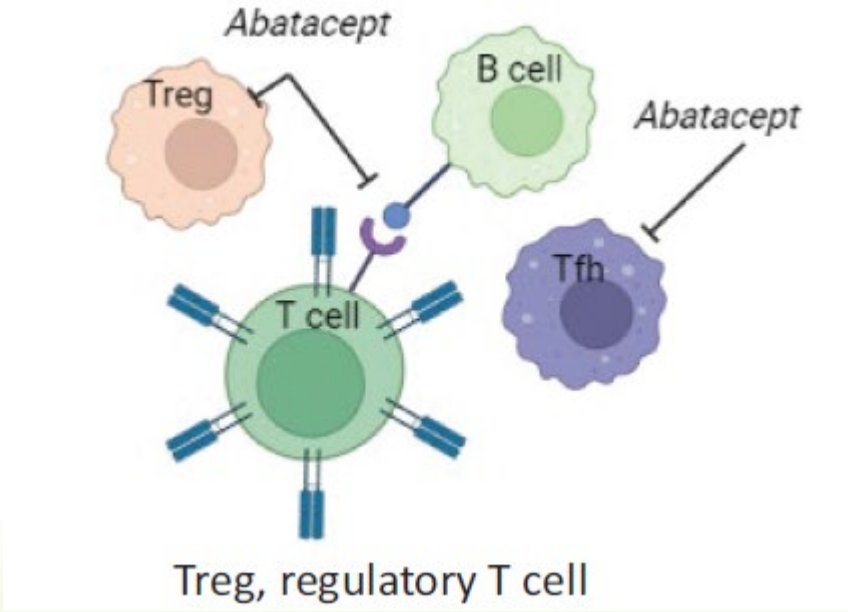
- **Stage 1:** ≥ 2 Autoantibodies to insulin, GAD65, IA-2 and/ or ZnT8
- **Stage 2:** autoantibodies AND dysgylcemia (impaired fasting glucose, impaired glucose tolerance and/ or A1c ≥ 5,7%
- **Stage 3:** symptomatic T1D
- **Stage 4:** long-standing T1D

Insel et al, Diabetes Care 2015;38:1964-74

Abatacept in the Prevention of T1D

Type 1 Diabetes TrialNet

- **Randomized, double-masked, controlled trial**
- **Objective:** to determine whether abatacept will prevent or delay the development of stage 2 T1D in at-risk, AB positive, non-diabetic relatives of T1D patients who have normal glucose tolerance (stage 1)
- 206 patients, Age ≥ 6 yrs, ≥ 2 AB positive, randomized 1:1 to abatacept or placebo for 12 mths
- **Primary outcome:** Hazard ratio for the development of AGT (stage 2) or T1D (stage 3)

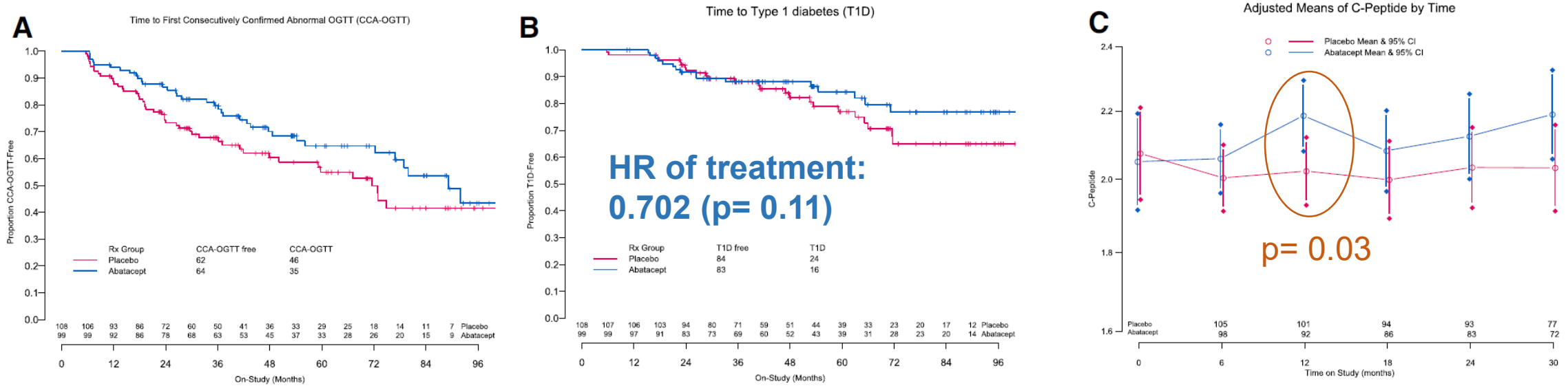


Co-stimulation modulation with Abatacept (CTLA4Ig) blocks the activation of T-cells and hence slows β-cell loss

Russell et al, Diabetes Care 2023;46(5):1005-1013

Abatacept in the Prevention of T1D

Type 1 Diabetes TrialNet



- No statistically significant delay in the progression to stage 2 or 3 type 1 diabetes
- Abatacept altered immune cell subsets and improved insulin secretion
- In a previous TrialNet study with Abatacept in newly diagnosed T1D, patients were treated for 2 y→ 59% higher C-Peptide and 9,6 month average delay in progression of insulin loss compared to those who received placebo→ longer treatment? Start in stage 2? Combining therapy?

Russell et al, Diabetes Care 2023;46(5):1005-1013
Orban et al, Lancet 2011 Jul 30;378(9789):412-19

Thank you for your attention