Paris NASH Meeting

International Think Tank

September 7 & 8, 2023

9th edition

Using drugs to achieve weight loss comparable to bariatrics

John Wilding, United Kingdom

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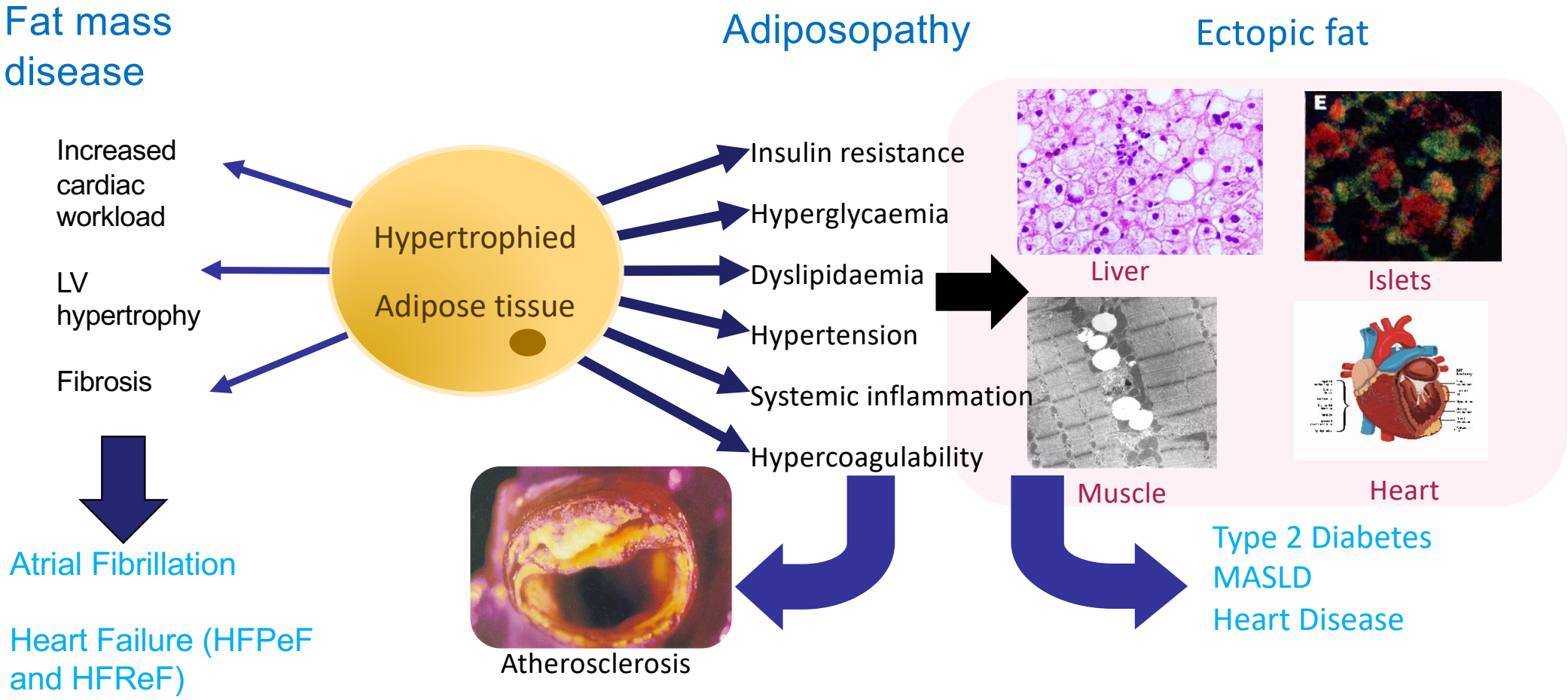
Conflict of interest disclosure

- **Consulting fees:** Paid to University of Liverpool - Alnylam, AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, Menarini, Mundipharma, Napp, Novo Nordisk, Pfizer, Prosciento, Rhythm Pharmaceuticals, Saniona, Shionogi, Tern, Ysopia
- **Research contracts:** Paid to University of Liverpool / Hospital – AstraZeneca, Novo Nordisk, Lilly, Rhythm Pharmaceuticals
- **Clinical trial steering committee:** AstraZeneca, Novo Nordisk, NIHR
- **Lecture Fees:** AstraZeneca, Boehringer Ingelheim, Napp, Novo Nordisk, Rhythm
- **Owner/stockholder of healthcare company/ies:** None
- **Other:** Trustee and Past president of World Obesity Federation (unpaid)

Obesity and MASLD are closely linked and associated with multiple complications



MASLD = Metabolic Dysfunction Associated Steatotic Liver Disease

Ayer J, et al. Eur Heart J. 2015;36:1371–6; Burke GL, et al. Arch Intern Med 2008; 168:928-35; WHO Global atlas on CVD. 2011; Church TS, et al. Gastroenterology 2006;130:2023–30.

Bariatric Surgery can improve NASH/MASLD

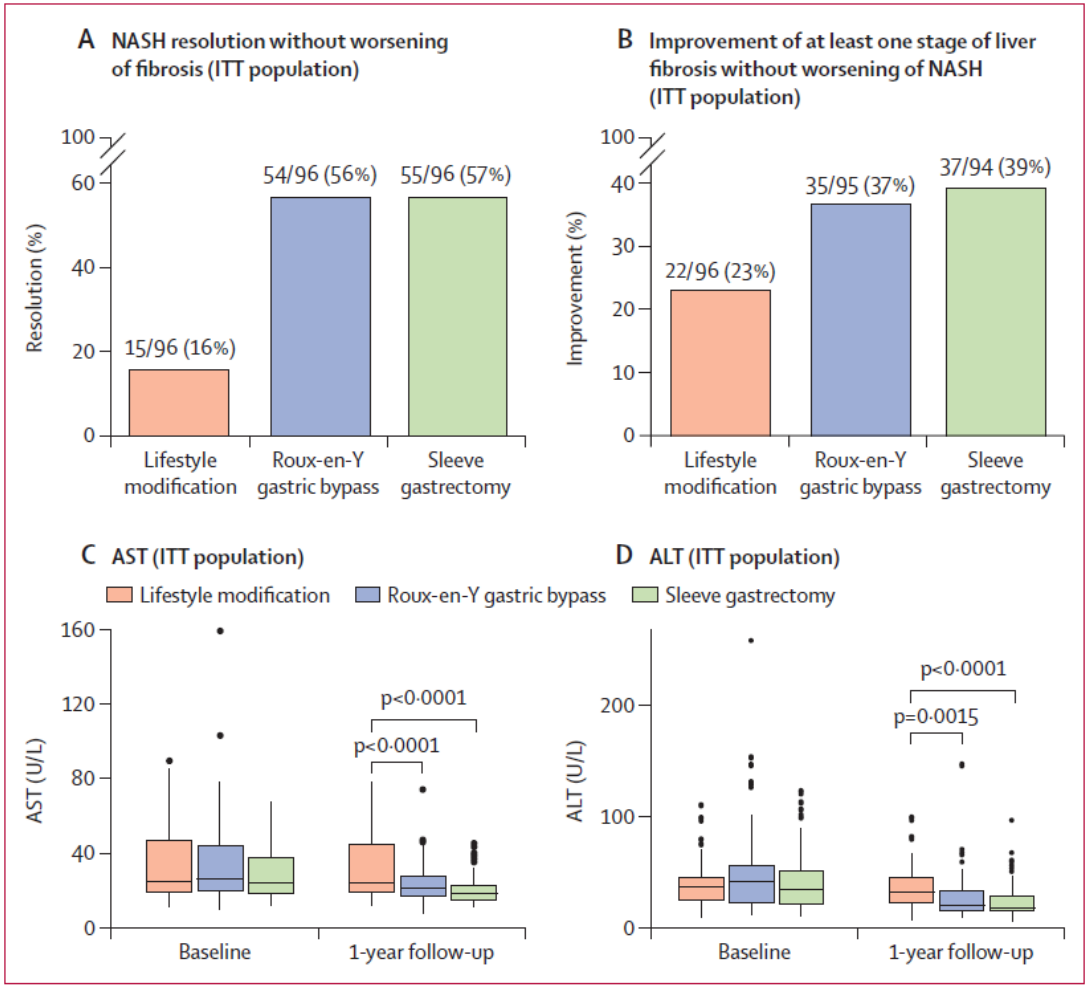


Figure 1: Primary endpoint, secondary endpoint, AST, and ALT results in the ITT population

Bariatric–metabolic surgery versus lifestyle intervention plus best medical care in non-alcoholic steatohepatitis (BRAVES): a multicentre, open-label, randomised trial

Ornella Verrastro*, Simona Panunzi*, Lidia Castagneto-Gissey, Andrea De Gaetano, Erminia Lembo, Esmeralda Capristo, Caterina Guidone, Giulia Angelini, Francesco Pennestrì, Luca Sessa, Fabio Maria Vecchio, Laura Riccardi, Maria Assunta Zocco, Ivo Boskoski, James R Casella-Mariolo, Pierluigi Marini, Maurizio Pompili, Giovanni Casella, Enrico Fiori, Francesco Rubino, Stefan R Bornstein, Marco Raffaelli, Geltrude Mingrone

Lancet 2023; 401: 1786–97

Summary

Background Observational studies suggest that bariatric–metabolic surgery might greatly improve non-alcoholic

Population: 288 people with biopsy-proven NASH

Open label RCT: lifestyle ± glucose lowering drugs vs sleeve gastrectomy vs RYGB

Key outcomes: NASH resolution, improvement in fibrosis stage, LFTs at one year

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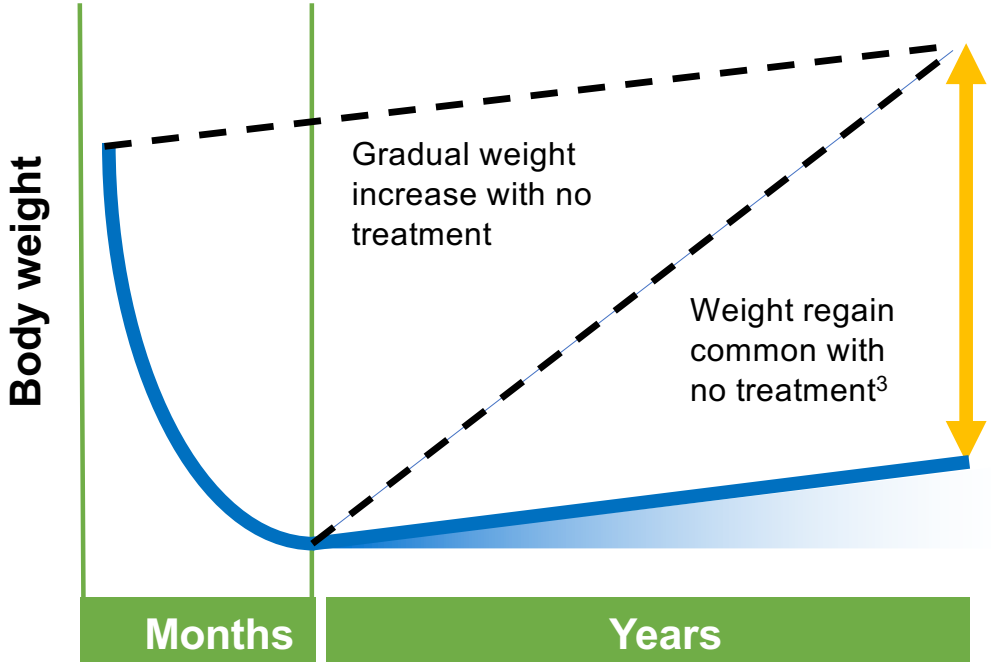
Goals and benefits of effective obesity management

1. Achieve weight loss[1,2]

2. Maintain weight loss and prevent regain[1,2]

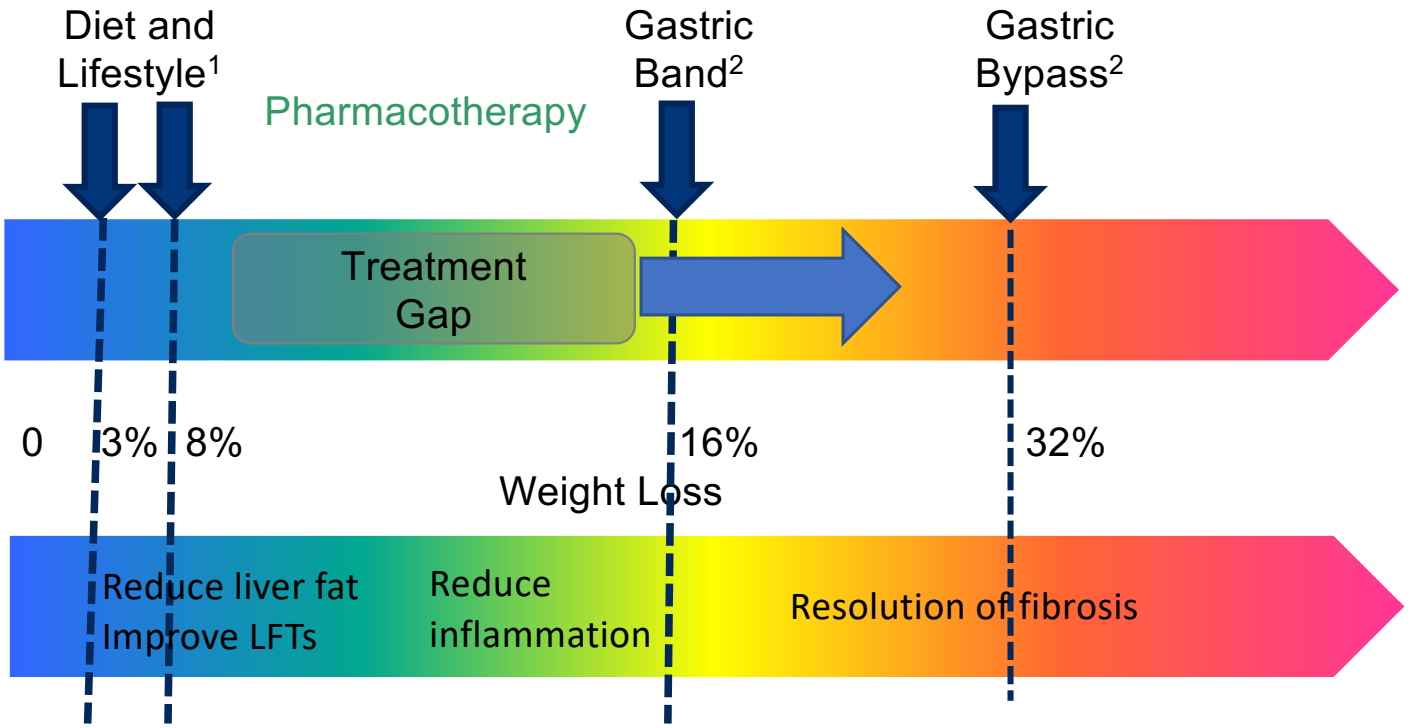


3. Provide clinically meaningful benefits[1]

- Reduce diabetes risk[1]
- Improve markers of cardiovascular risk[1]
- Improve other diseases – eg MASLD / NASH
- Reduce functional impairment[4]
- Improve quality of life[4]

1. Wadden *et al*. *Circulation* 2012;125:1157–70; 2. Jensen *et al. J Am Coll Cardiol* 2014;63(25 Pt B):2985–3023*;*
3. Purcell *et al*. *Lancet Diabetes Endocrinol* 2014;2:954–62; 4. Villareal *et al. Am J Clin Nutr* 2005;82:923–34.

Obesity treatment: How much weight loss needed to improve MASLD?



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Approved drug treatments for weight management

European Union (&UK) : 2023

Orlistat 60/120 mg TDS
(Alli®/Xenical®)

Naltrexone 32 mg/ Bupropion 360 mg PR[3]
(Mysimba™)
PR, prolonged release

Liraglutide 3.0 mg daily
(Saxenda®)

Metreleptin od

Semaglutide 2.4 mg Weekly
(Wegovy®)

Setmelanotide 1-3mg od
IMCIVREE®

Metreleptin – only for leptin deficiency; Semaglutide – not yet widely available; Setmelanotide – only for POMC deficiency, LEPR, MC4R genetic causes

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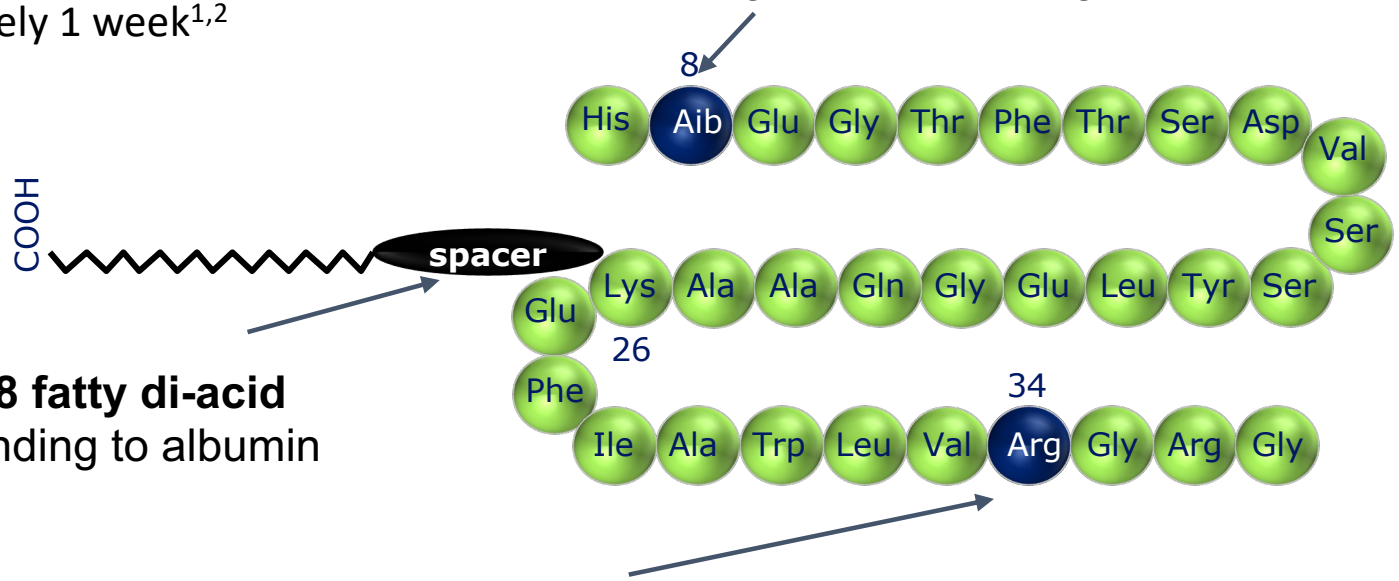
Semaglutide

- 94% homology to human GLP-1[1]
- Modifications prolong the half-life of semaglutide to approximately 1 week[1,2]

Amino acid substitution
protects against DPP-4 degradation



Spacer and C-18 fatty di-acid
provides strong binding to albumin

Amino acid substitution
prevents side chain binding at wrong site

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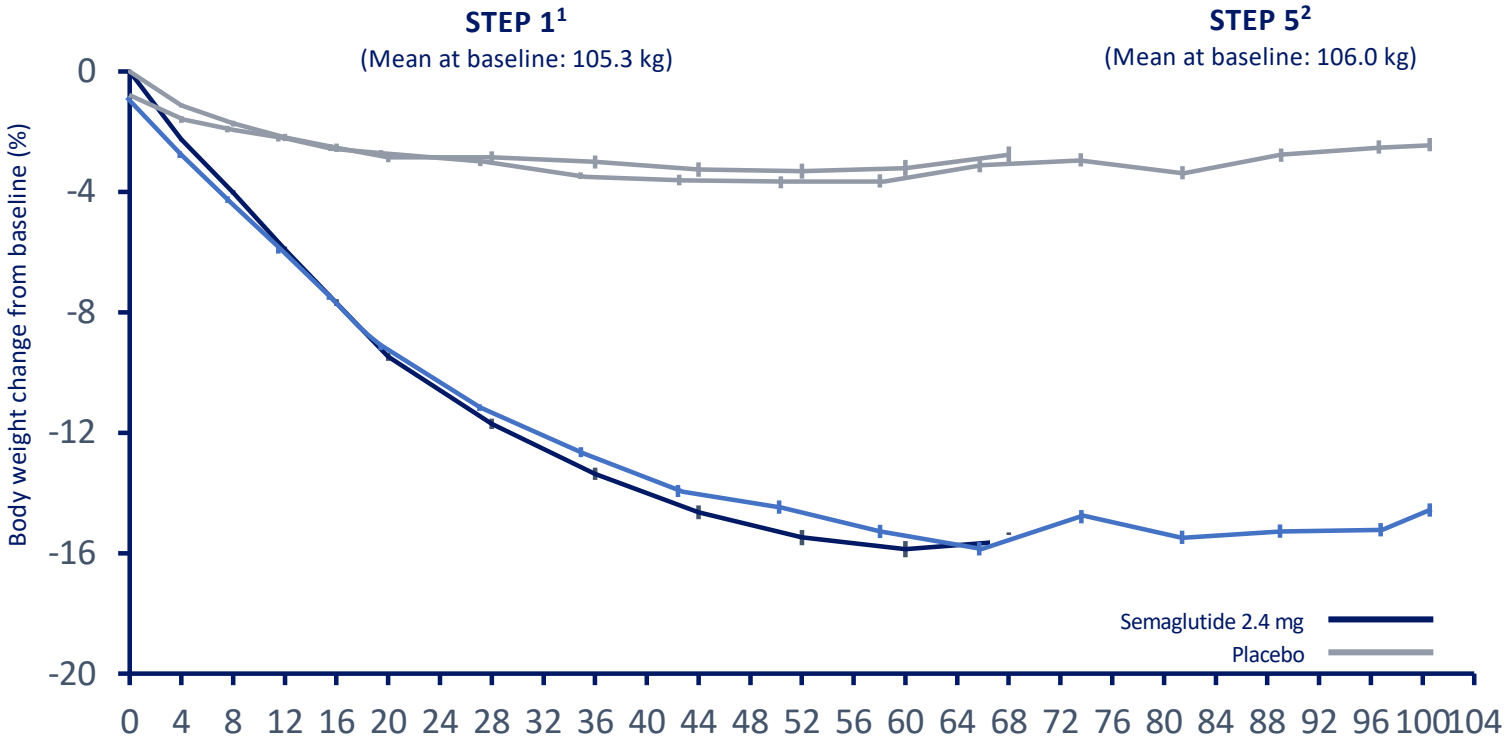
- DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1.
1. Kapitza C et al. J Clin Pharmacol 2015;55:497–504; 2. Marbury TC et al. Diabetologia 2014;57(Suppl. 1):S358.

Semaglutide 2.4mg weekly for obesity

Change in body weight over time: STEP 1 vs STEP 5



1. Wilding et al. N Engl J Med 2021;384:989−1002; 2. Garvey et al. Presented at the 39th Annual Meeting of The Obesity Society held at ObesityWeek®, virtual meeting, November 1–5, 2021

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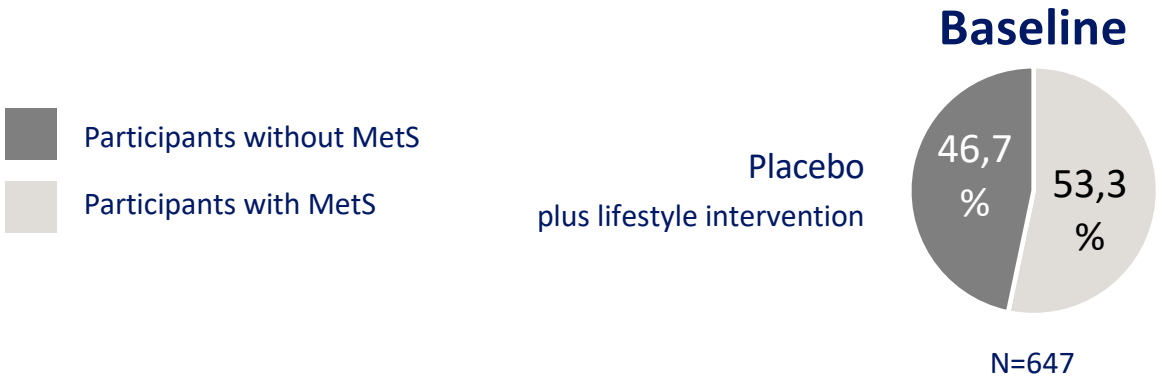
STEP 1: Prevalence of metabolic syndrome

Proportion of participants with MetS at baseline and at Week 68



Metabolic syndrome was defined using the NCEP ATP III criteria. MetS, metabolic syndrome; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III

le Roux CW et al. Presented at the European and International Congress on Obesity (ECO) virtual meeting, May 10–13, 2021

Safety summary with semaglutide 2.4 mg in people with obesity

- Semaglutide 2.4 mg appeared be well-tolerated and has an established safety profile[1-3]

- The most common adverse events among people treated with semaglutide 2.4 mg were gastrointestinal events[1-3]
  - Most were transient, and mild or moderate in severity

- Three participants had mild acute pancreatitis and 1 had gallstones in STEP 1[1]

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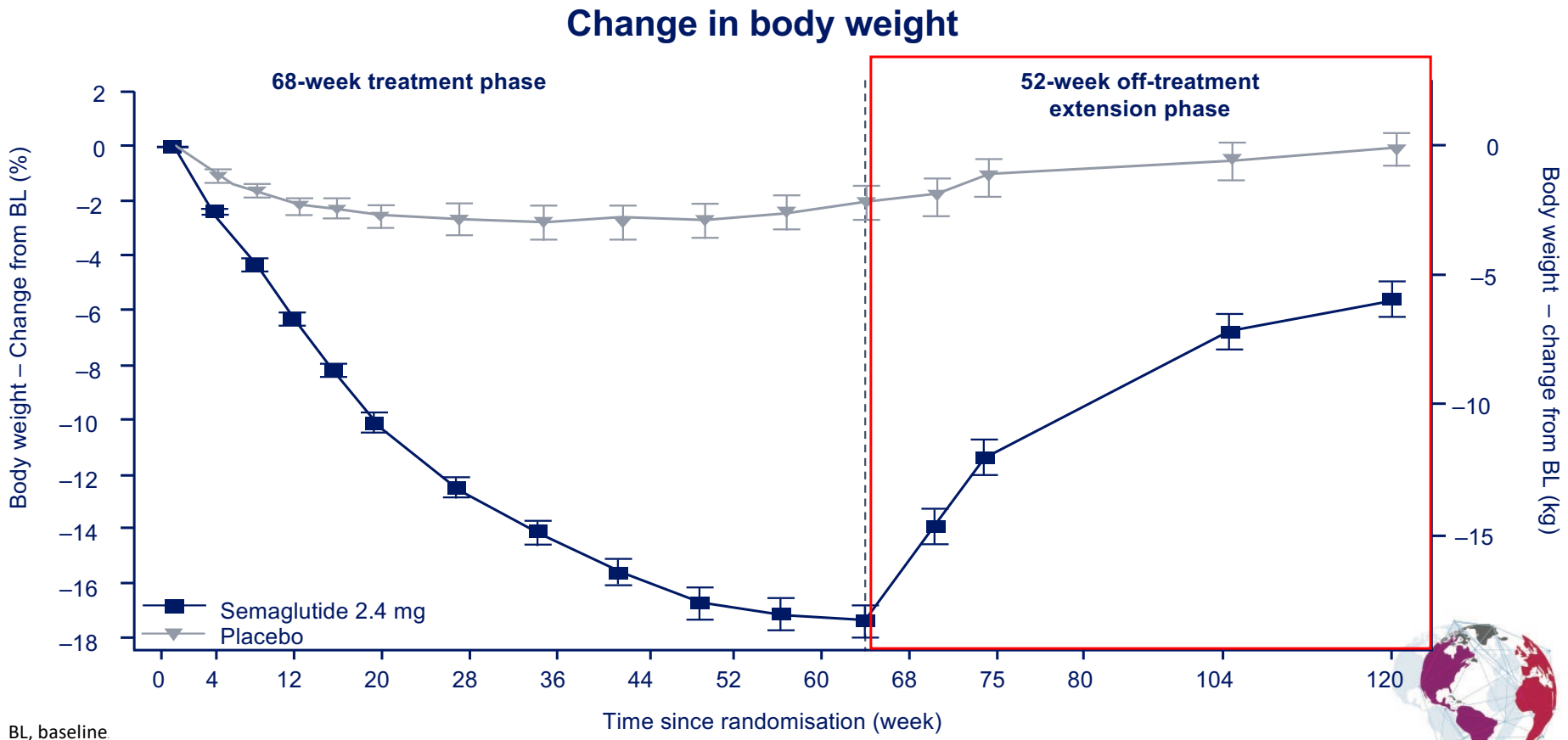
1. Wilding et al. N Engl J Med 2021;384:989−1002; 2. Rubino et al. 2021;325:1414−25; 3. Garvey et al. Presented at the 39th Annual

STEP 1 observational extension
Weight regain is common after treatment cessation
Obesity is a chronic disease that requires long-term management



- BL, baseline.
- Wilding et al. *Diabetes Obes Metab* 2022;24:1553–64.

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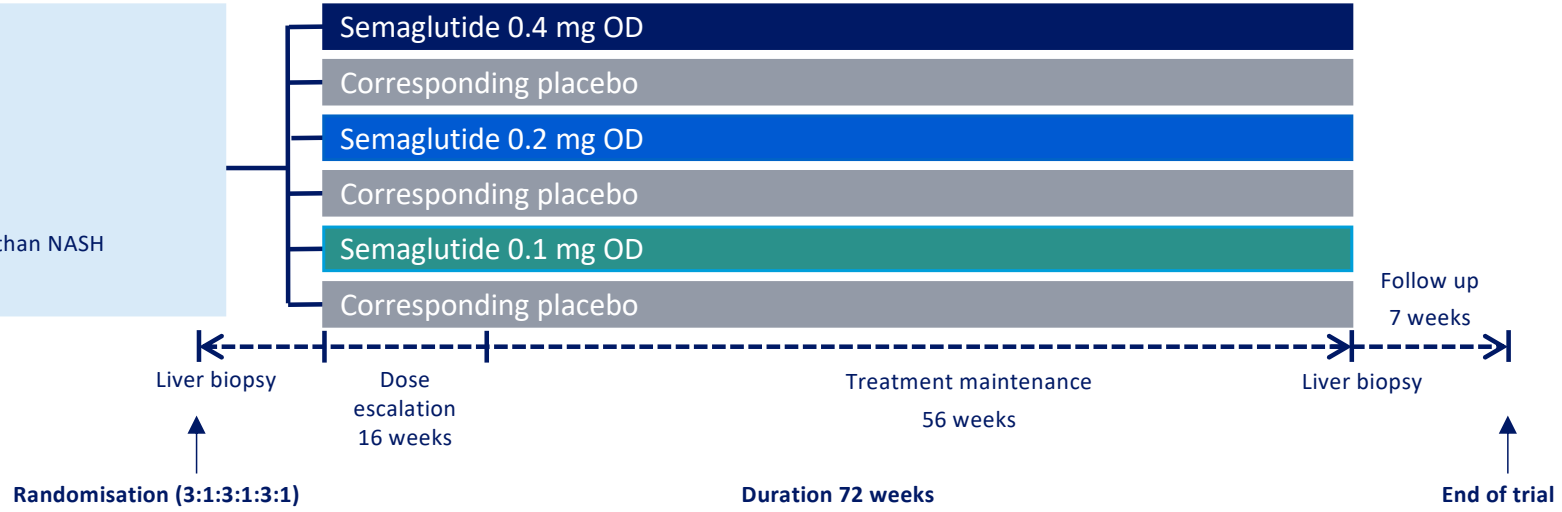
Semaglutide is not approved for treatment of NASH

Sema-NASH phase 2: trial design

72-week randomised, placebo-controlled trial

320 patients

- Age 18–75 years
- NAS ≥4
- NASH fibrosis stage 1, 2 or 3
- BMI >25.0 kg/m^2
- HbA_{1c} ≤10%
- No chronic liver disease other than NASH



Trial objective

To compare the effect of semaglutide versus placebo on histological resolution of NASH

Key endpoints

- **Primary:** Resolution of steatohepatitis and no worsening in liver fibrosis in subjects with fibrosis*
- **Confirmatory secondary**: Improvement in liver fibrosis and no worsening in steatohepatitis†

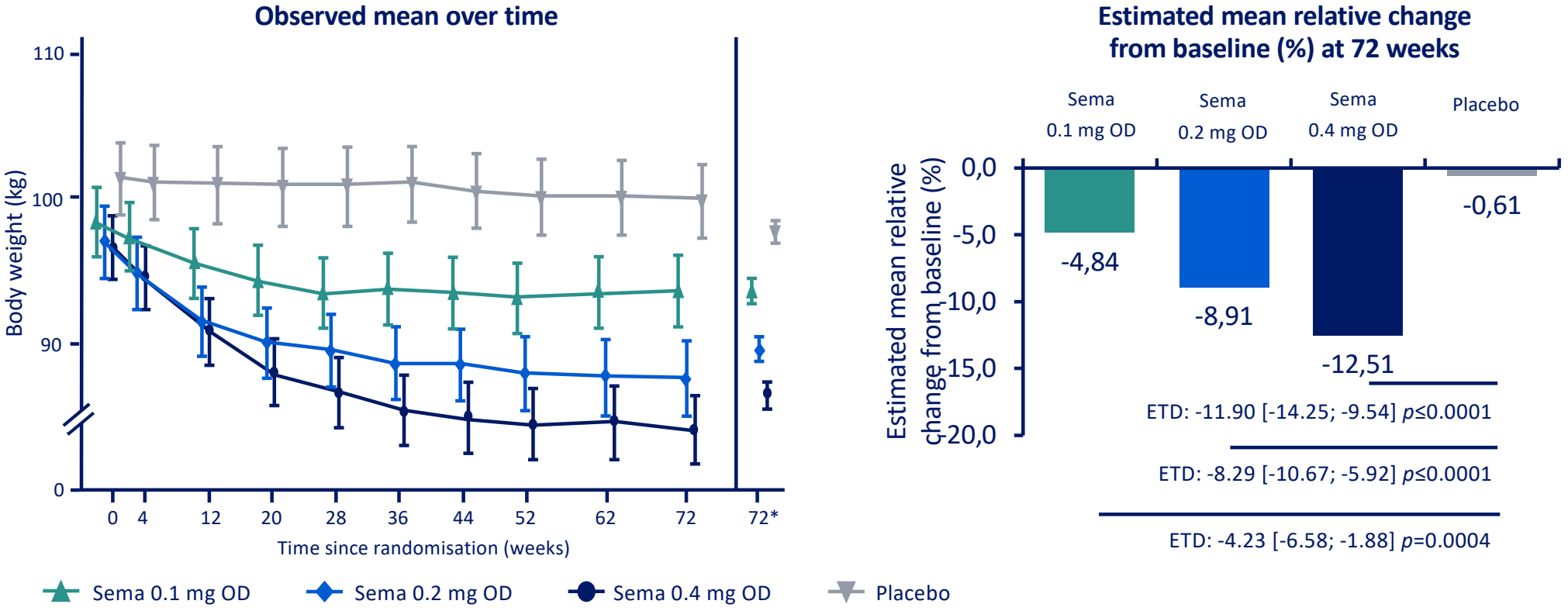
**Resolution of steatohepatitis defined by the NASH clinical research network (CRN) as no more than mild residual inflammatory cells (0–1) and no ballooning (0). Fibrosis was graded on the NASH CRN fibrosis scale from 0 to 4. Primary analysis to assess efficacy in patients with stage 2 and 3 fibrosis. †Worsening of steatohepatitis as defined as an increase of at least one stage of either lobular inflammation or hepatocyte ballooning according to NASH CRN criteria.*

BMI, body mass index; HbA_{1c}, glycated haemoglobin; NAFLD, non-alcoholic fatty liver disease; NAS, NAFLD activity score; NASH, non-alcoholic steatohepatitis OD, once-daily.

Harrison SA et al. Contemp Clin Trials. 2020;doi:10.1016/j.cct.2020.106174; Newsome PN et al. N Engl J Med 2020. doi: 10.1056/NEJMoa2028395.

Sema-NASH phase 2: Change in body weight

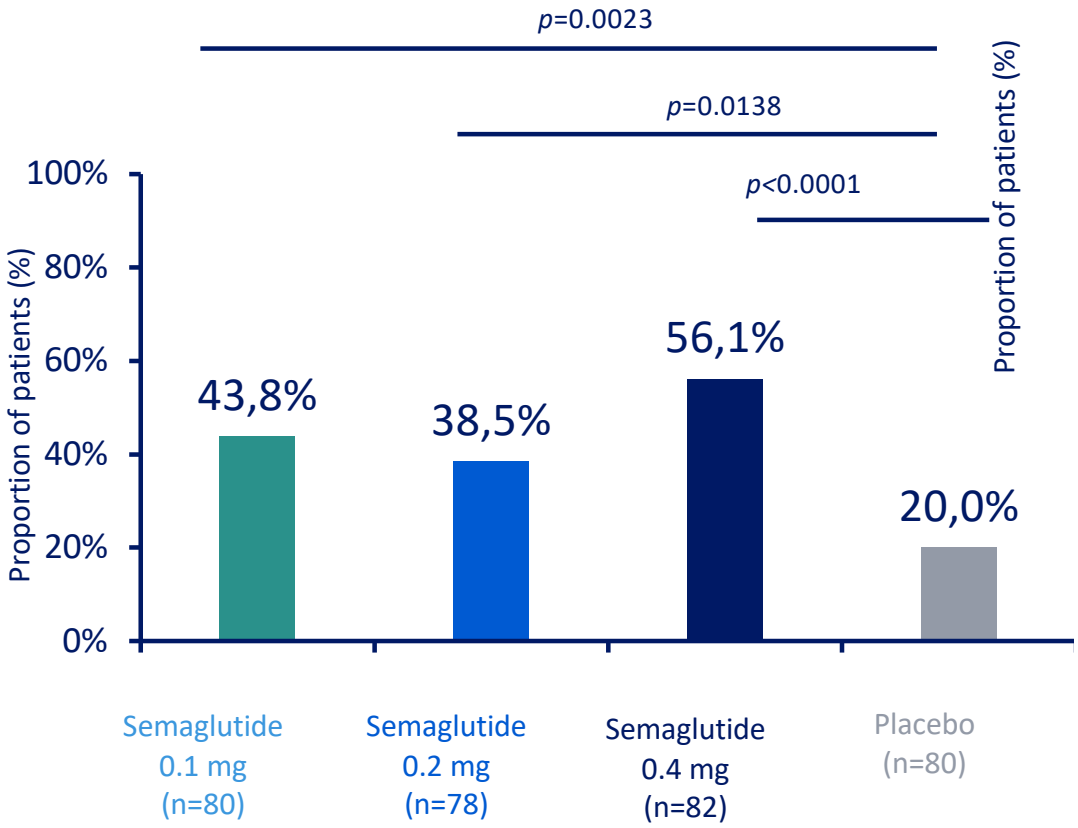
All randomised subjects



*Data based on in-trial period, all randomised subjects. *Estimates taken from an ANCOVA with missing data multiply imputed from placebo group. ANCOVA, analysis of covariance; OD, once-daily; sema, semaglutide. Newsome PN et al. N Engl J Med 2020. doi: 10.1056/NEJMoa2028395.*

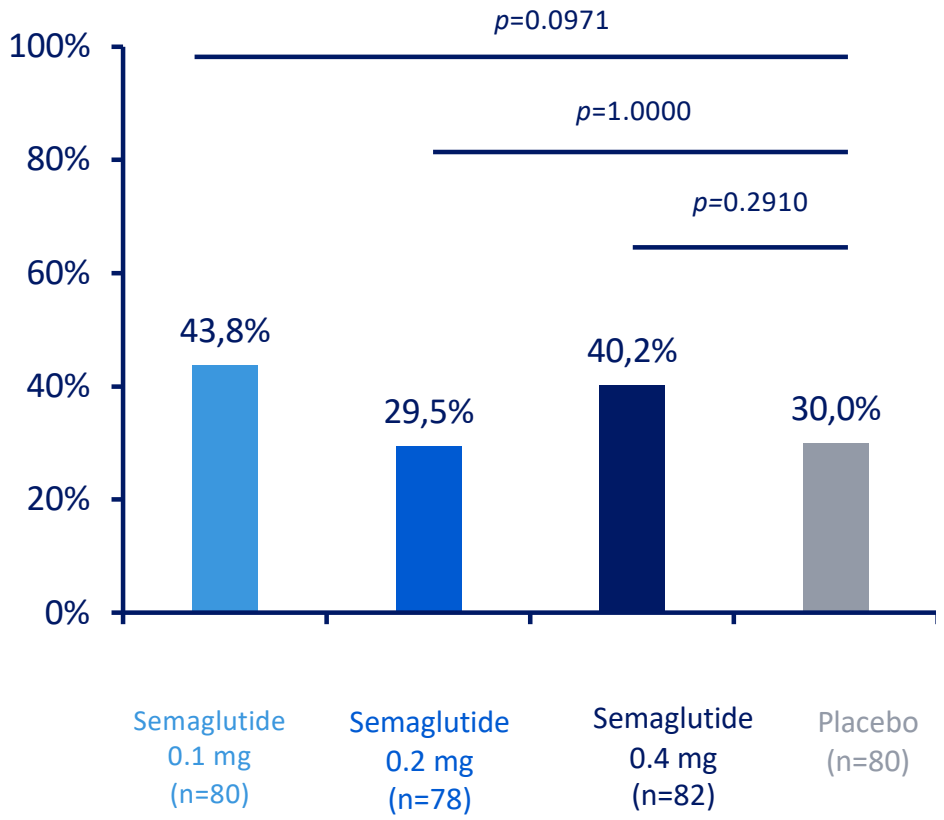
Resolution of steatohepatitis and no worsening in liver fibrosis

All randomised subjects



Improvement in liver fibrosis and no worsening in steatohepatitis

All randomised subjects



Data based on in-trial period. Two-sided p-values from a Cochran-Mantel-Haenszel test. Subjects with missing data handled as non-responders.
Newsome PN et al. N Engl J Med 2020. doi: 10.1056/NEJMoa2028395.

Semaglutide: too late in established cirrhosis?

Semaglutide 2·4 mg once weekly in patients with non-alcoholic steatohepatitis-related cirrhosis: a randomised, placebo-controlled phase 2 trial

Rohit Loomba, Manal F Abdelmalek, Matthew J Armstrong, Maximilian Jara, Mette Skalshøi Kjær, Niels Krarup, Eric Lawitz, Vlad Ratziu, Arun J Sanyal, Jörn M Schattenberg, Philip N Newsome*, on behalf of the NN9931-4492 investigators†*

Summary

Background Patients with non-alcoholic steatohepatitis (NASH)-related cirrhosis are at high risk of liver-related and all-cause morbidity and mortality. We investigated the efficacy and safety of the glucagon-like peptide-1 analogue semaglutide in patients with NASH and compensated cirrhosis.

Lancet Gastroenterol Hepatol 2023; 8: 511–22

Published Online March 16, 2023

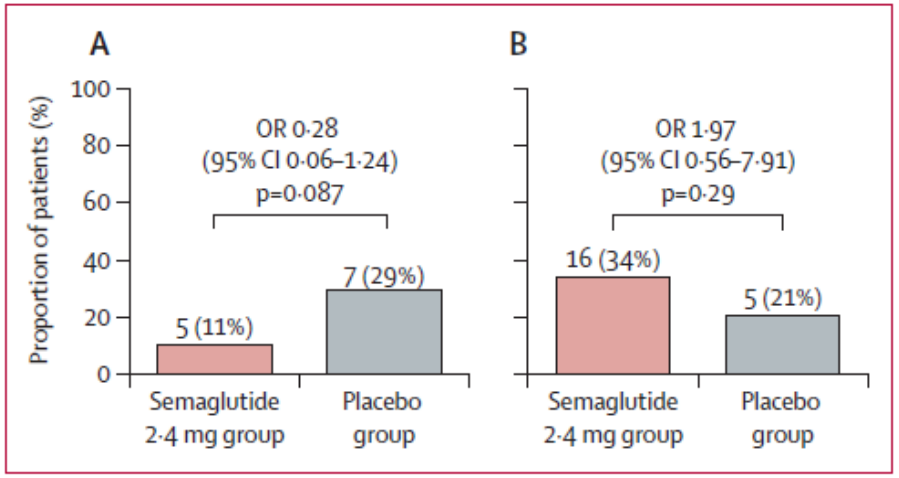


Figure 2: **Improvement in liver fibrosis and no worsening of NASH (A) and resolution of NASH (B) at 48 weeks**

p-values are two-sided and taken from a Cochran–Mantel–Haenszel test stratified by baseline diabetes status. Patients with missing outcomes were imputed as non-responders. NASH=non-alcoholic steatohepatitis. OR=odds ratio.

71 patients (75% with T2DM); with biopsy proven NASH and cirrhosis

Randomised 2:1 semaglutide 2.4mg weekly or placebo for 48 weeks

Successful weight loss and reductions in HbA1c in those with T2DM; improvements in liver fat and biochemical liver function tests (eg ALT).

No effect on improvement in fibrosis or resolution of NASH

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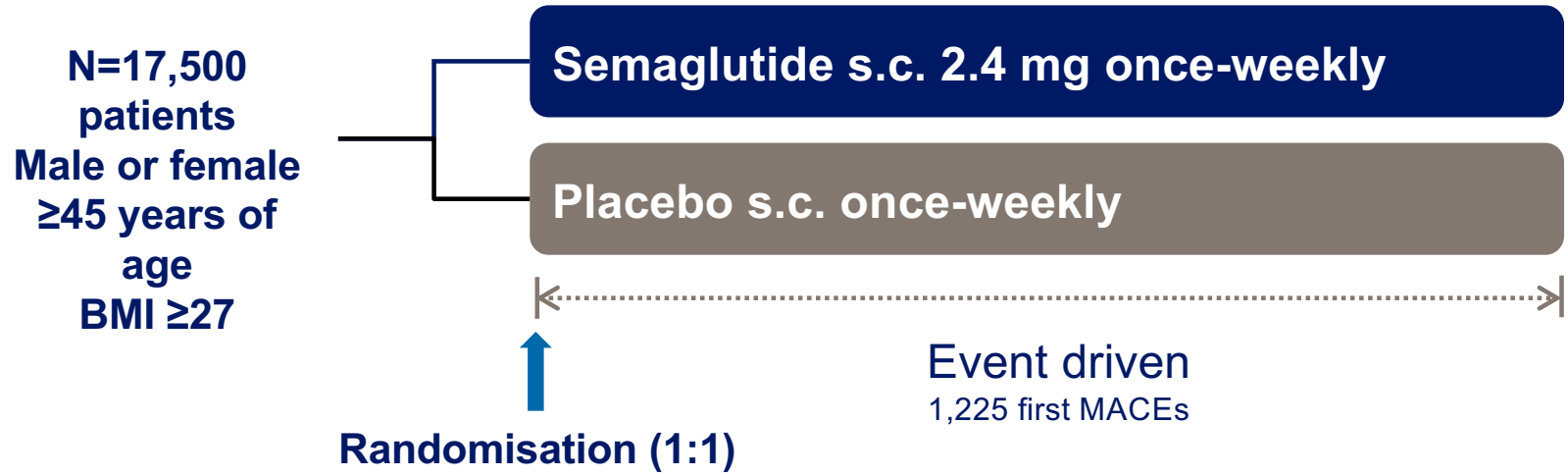
SELECT clinical trial: GLP-1RA in high CVD risk overweight/obesity without diabetes



Prior MI | Prior stroke | PAD

Primary endpoint:
Time from randomisation to first occurrence of a composite endpoint consisting of either:

- CV death
- Non-fatal myocardial infarction
- Non-fatal stroke

STOP Press: Novo Company Announcement 8/8/2023:
Semaglutide associated with 20% reduction in primary outcome in SELECT trial

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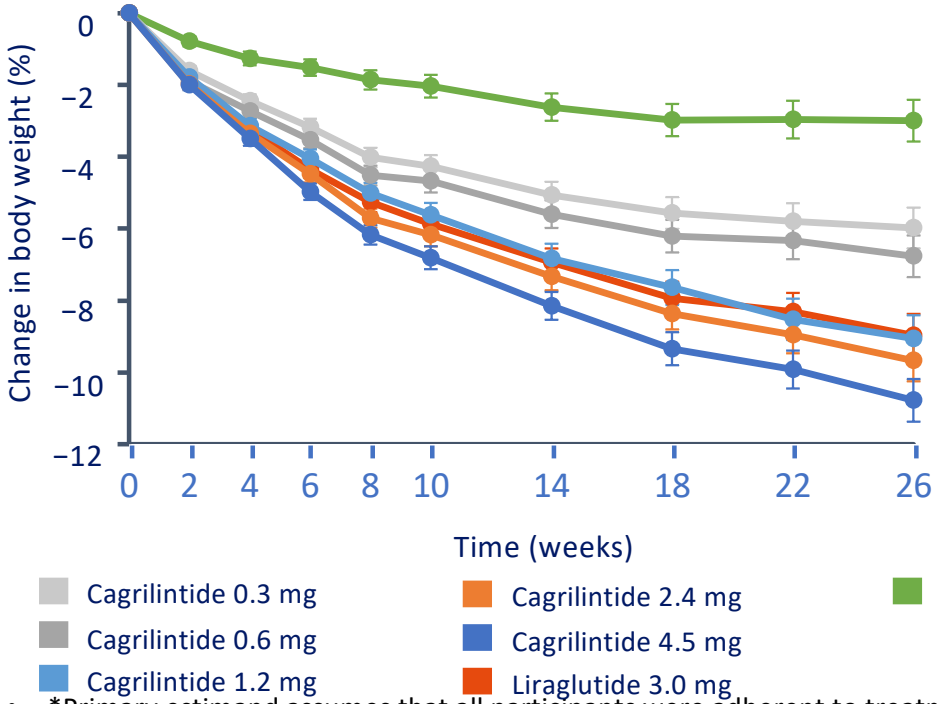
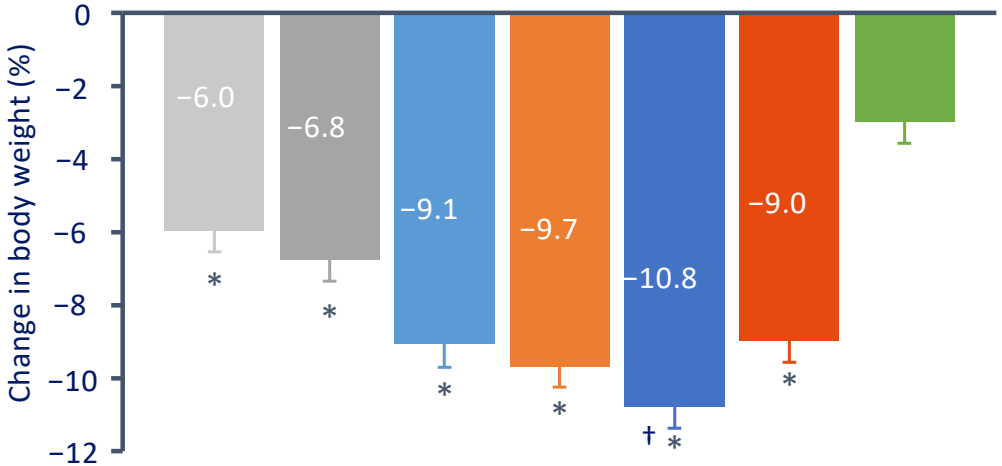
Future prospects – can we match surgery with drugs?

- Triple agonism using GLP-1, GIP, glucagon
- GIP agonists or antagonists?
- Other combinations – PYY, ghrelin antagonists?
- Oral options (high dose semaglutide, danuglipron, orforglipron)

Amylin agonist (cagrilintide) phase 2 trial: Change in body weight (%)

- Baseline to week 26 – Primary estimand*





vs placebo
*p<0.001

vs liraglutide
†p<0.05 in favour of cagrilintide

- *Primary estimand assumes that all participants were adherent to treatment. Mean (SEM) change from baseline in body weight (%) by treatment week
  – MAR-MI – treatment adherent – full analysis set. ANCOVA estimates using the primary analysis.
- ANCOVA, analysis of covariance; MAR-MI, missing at random multiple imputation; SEM, standard error of the mean.
- Batterham RL, et al. Poster/oral 099, ECO2021, May 10–13, 2021.

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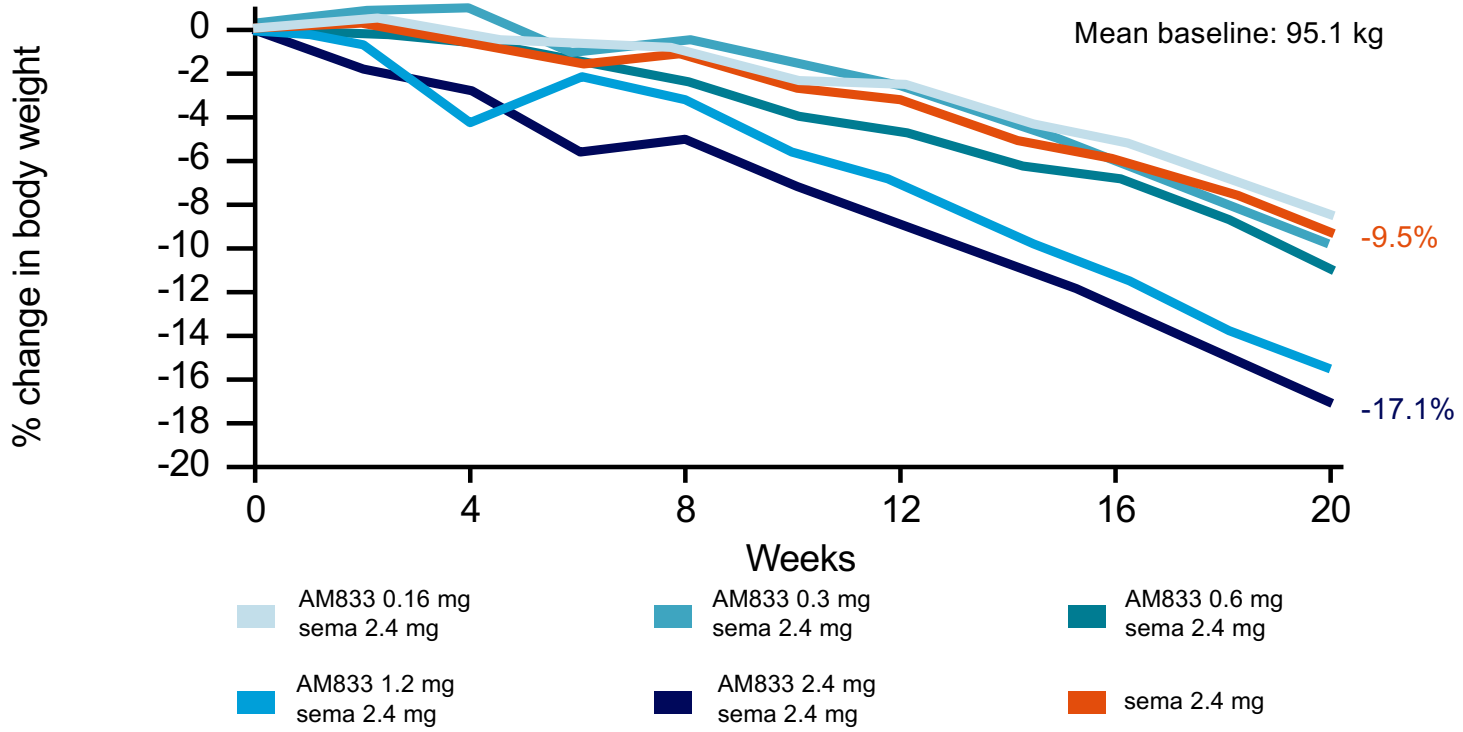
Weight loss with semaglutide & amylin agonist

Cagrilintide & semaglutide phase I trial



66% of people on AM833 + semaglutide 2.4 mg achieved >15% weight loss in 20 weeks

Enebo et al Lancet 2021
https://www.novonordisk.com/content/nncorp/global/en/news-and-media/news-and-ir-materials/news-details.html?id=274

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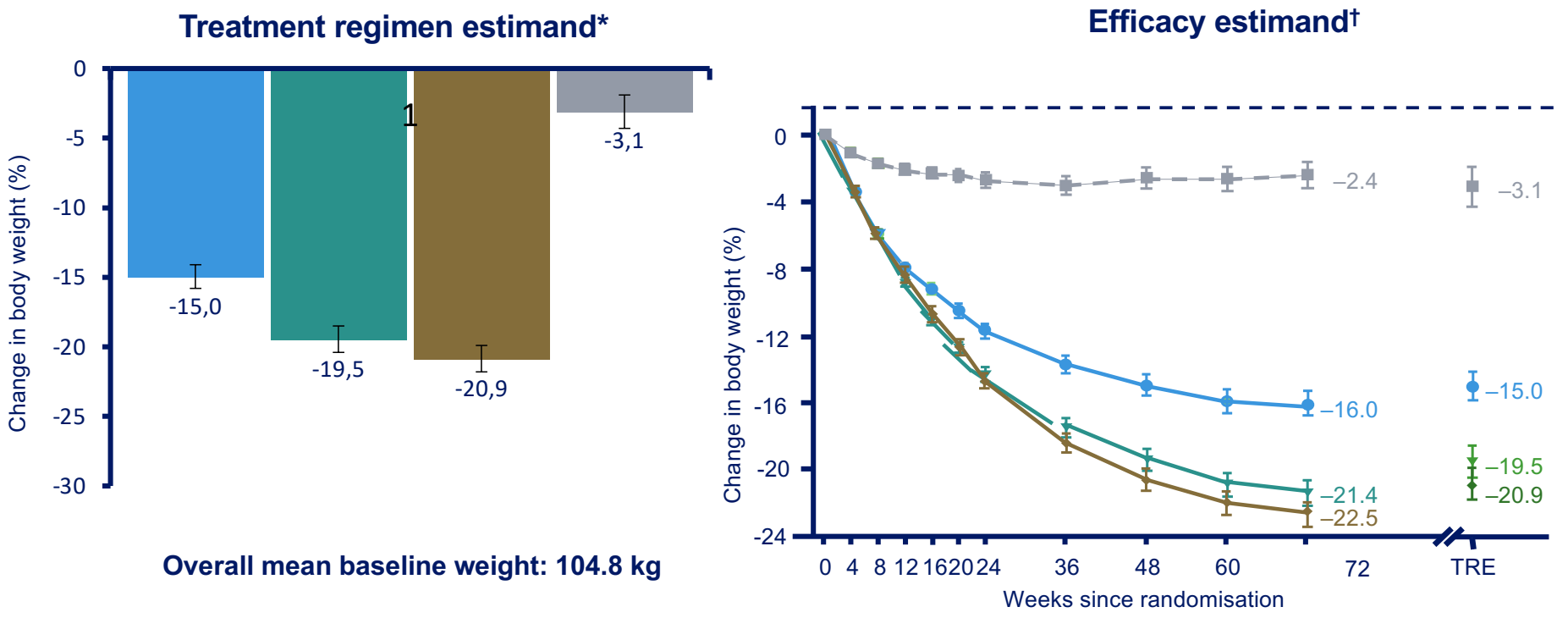
SURMOUNT 1 (tirzepatide for treatment of obesity) Change in body weight from baseline to Week 72 (co-primary endpoint)



Figures show least-squares means, ±95% confidence intervals. *Treatment policy estimand baseline to Week 72. †Trial product estimand. Treatment-regimen estimand represents average treatment effect of tirzepatide relative to placebo for all randomised participants, regardless of treatment discontinuation. Efficacy estimand represents average treatment effect of tirzepatide relative to placebo for all randomised participants if treatment administered as intended.
OW, once weekly; TRE, treatment regimen estimand.
Jastreboff et al. *N Engl J Med* 2022;387:205–16.

SURMOUNT-1: Tirzepatide in people with obesity and no diabetes – CV risk factors

	Tirzepatide 5 mg (n=630)	Tirzepatide 10 mg (n=636)	Tirzepatide 15 mg (n=630)	Placebo (n=643)
Change in:				
SBP (mmHg)	–7.0 (–7.9, –6.1)	–8.2 (–9.1, –7.3)	–7.6 (–8.5, –6.7)	–1.2 (–2.1, –0.3)
DBP (mmHg)	–5.2 (–5.8, –4.6)	–5.5 (–6.1, –4.9)	–4.6 (–5.2, –4.0)	–1.0 (–1.7, –0.3)
Waist circumference (cm)	–14.6	–19.4	–19.9	–3.4
% change in:				
Triglycerides (mg/dL)	–24.3 (–26.6, –22.0)	–27.0 (–29.3, –24.7)	–31.4 (–33.5, –29.3)	–6.3 (–9.3, –3.3)
Non-HDL cholesterol (mg/dL)	–9.5 (–11.1, –7.9)	–11.0 (–12.6, –9.4)	–13.4 (–15.0, –11.8)	–1.8 (–3.7, 0.09)
HDL cholesterol (mg/dL)	7.0 (5.5, 8.5)	8.6 (7.1, 10.1)	8.2 (6.7, 9.7)	0.2 (–1.2, 1.7)
Total cholesterol (mg/dL)	–4.9 (–6.2, –3.7)	–5.6 (–6.8, –4.4)	–7.4 (–8.6, –6.2)	–1.1 (–2.5, 0.2)
LDL cholesterol (mg/dL)	–5.3 (–7.2, –3.4)	–6.6 (–8.5, –4.7)	–8.6 (–10.5, –6.8)	–0.9 (–3.0, 1.3)
VLDL cholesterol (mg/dL)	–24.2 (–26.5, –21.9)	–26.7 (–28.9, –24.5)	–31.7 (–33.8, –29.6)	–5.6 (–8.6, –2.6)

•Data shown are least squares mean and 95% CI, except for waist circumference that shows mean change. All data show the efficacy estimand. Efficacy estimand represents average treatment effect of tirzepatide relative to placebo for all randomised participants if treatment administered as intended.
CV, cardiovascular; DBP, diastolic blood pressure; SBP, systolic blood pressure; VLDL, very low-density lipoprotein.
Jastreboff et al. *N Engl J Med* 2022;387:205–16 (and supplementary appendix).

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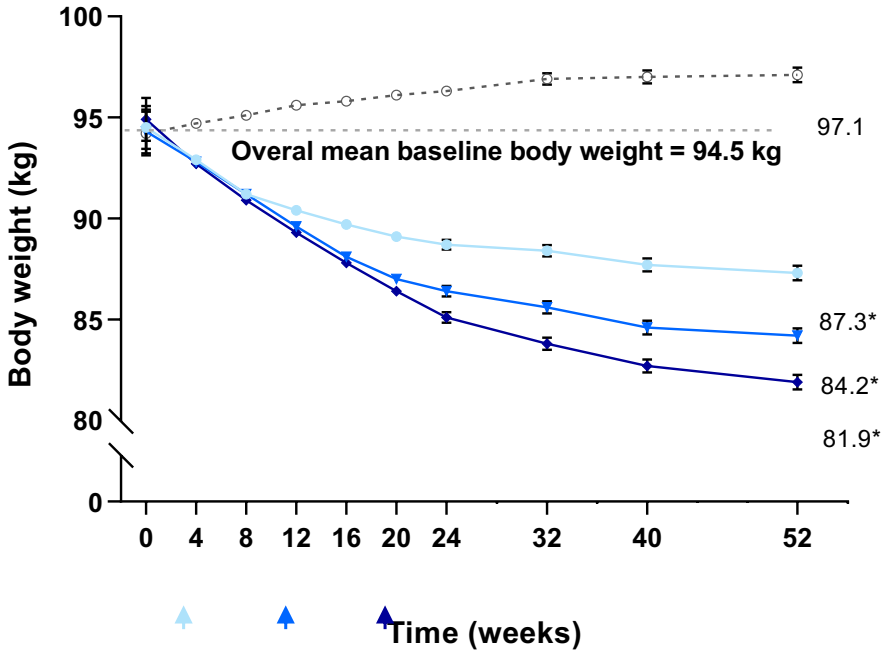
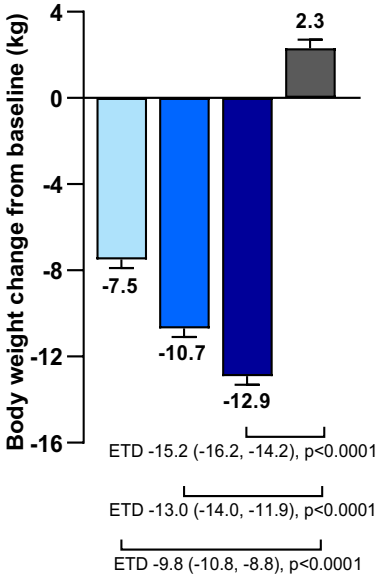
Tirzepatide in T2DM: Change in body weight at week 52

SURPASS-3

Body Weight Over Time from Baseline at Week 52 (Efficacy Estimand)



Change from Baseline in Body Weight at Week 52 (Efficacy Estimand)

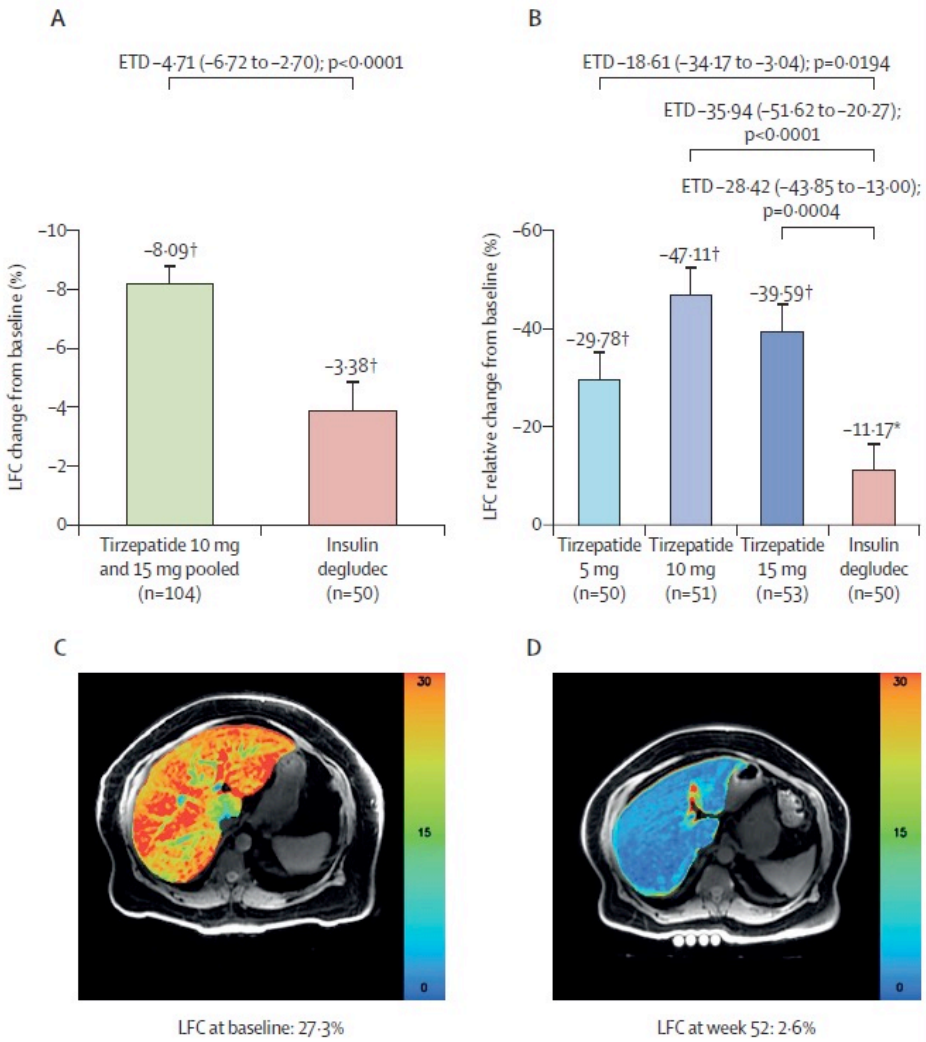


Note: Data are LSM (SE) from a MMRM analysis; mITT population (efficacy analysis set). ETD versus insulin degludec are LSM (95% CI) at Week 52. Arrows indicate when the maintenance dose of tirzepatide 5, 10, and 15 mg are initiated for the respective treatment groups. Estimated treatment difference (95% CI) of tirzepatide vs. insulin degludec was: i) 5 mg, -9.8 kg* (-10.8, -8.8); ii) 10 mg, -13.0 kg* (-14.0, -11.9); and iii) 15 mg, -15.2 kg* (-16.2, -14.2). *p<0.001 vs. insulin degludec.

CI=Confidence Interval; ETD=Estimated Treatment Difference; LSM=Least Squares Mean; mITT=Modified Intent-to-Treat; MMRM=Mixed Model Repeated Measures; SE=Standard Error.

Ludvik B, et al. Lancet. 2021;398(10300):583-598.

SURPASS 3 MRI substudy



Effect of tirzepatide versus insulin degludec on liver fat content and abdominal adipose tissue in people with type 2 diabetes (SURPASS-3 MRI): a substudy of the randomised, open-label, parallel-group, phase 3 SURPASS-3 trial

Amalia Gastaldelli, Kenneth Cusi, Laura Fernández Landó, Ross Bray, Bram Brouwers, Ángel Rodríguez

Summary

Background Tirzepatide is a novel dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 receptor agonist under development for the treatment of type 2 diabetes. The aim of this substudy was to characterise

Lancet Diabetes Endocrinol 2022; 10: 393-406

296 of patients in SURPASS 3 included

Key outcomes: changes in liver fat and body composition

Both central adiposity (data not shown here) & liver fat were reduced with tirzepatide treatment compared to insulin degludec

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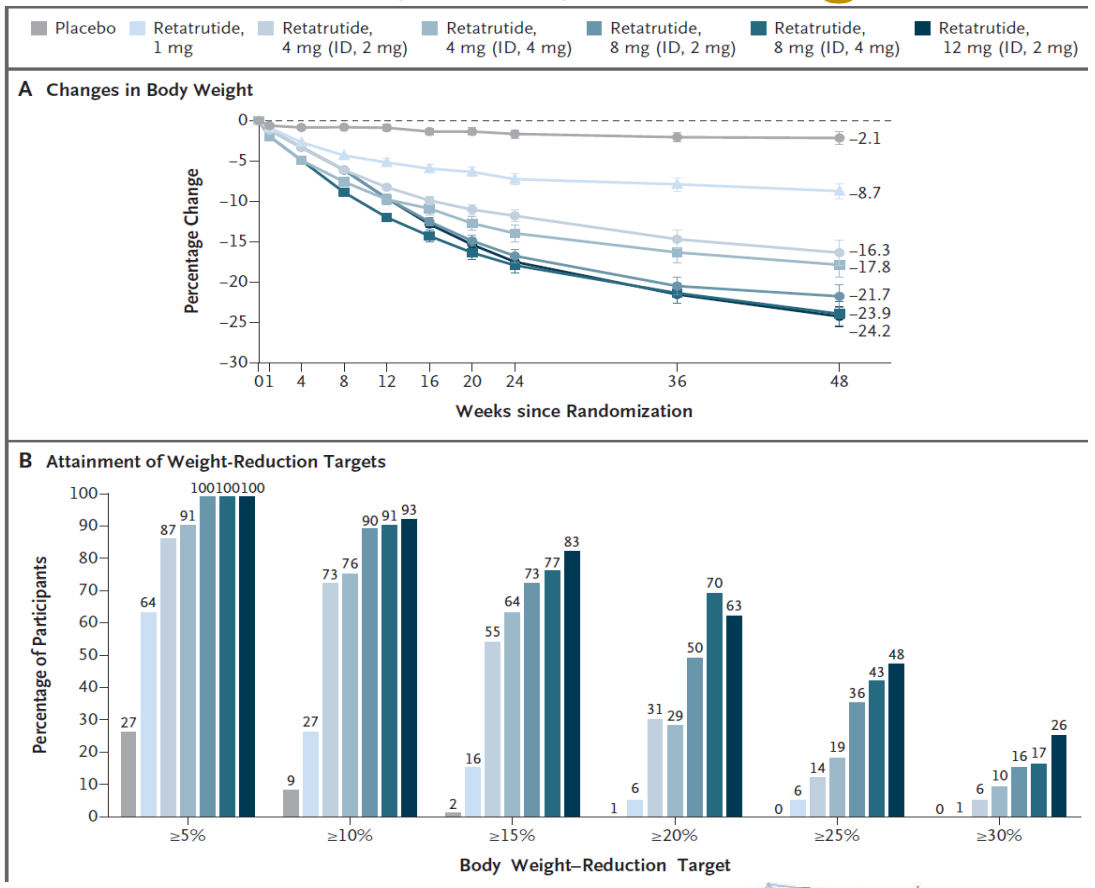
Triple agonist retadrutide – GLP1, GIP, Glucagon

- Phase 2, double blind, placebo controlled trial of triple agonist
- 338 participants; 51.8% men
- All received dietary / lifestyle advice
- 24% weight loss with highest dose
- CV risk factors (BP, lipids, glucose) - all improved
- Adverse effects – GI – similar to GLP1RA, less with lower starting doses; small rises in heart rate.



- Jastreboff et all NEJM 2023 DOI: 10.1056/NEJMoa2301972

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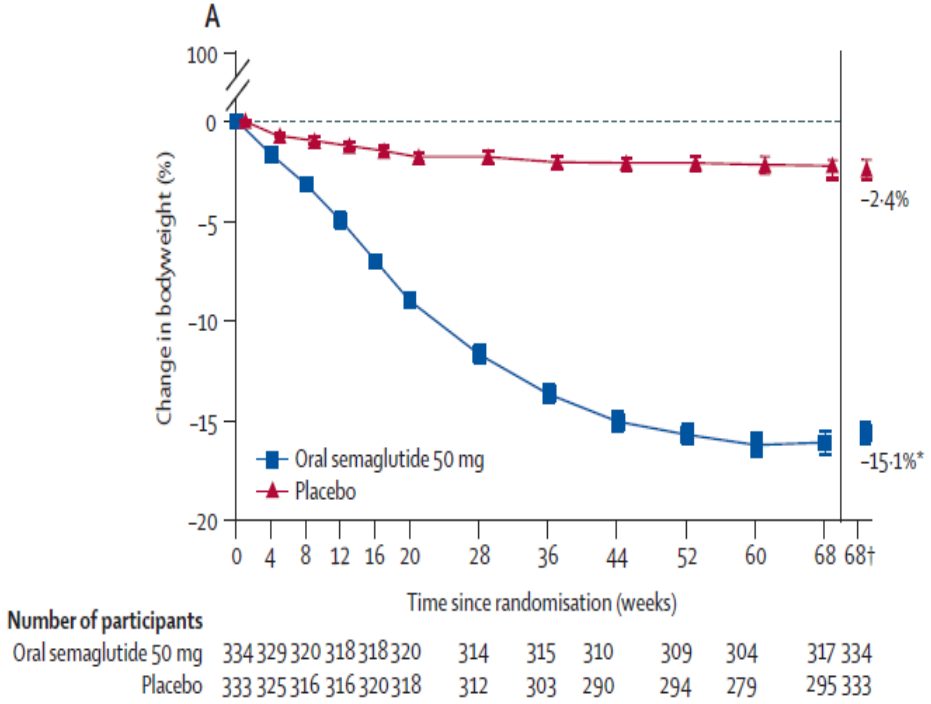
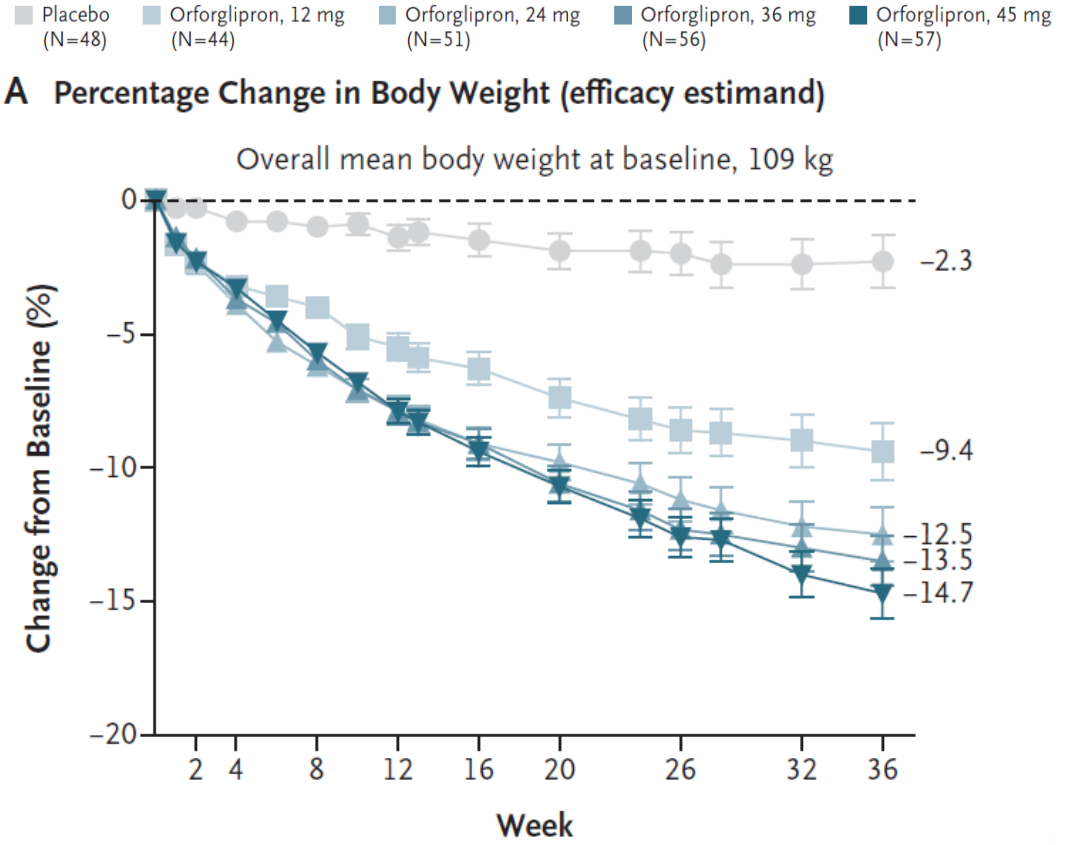
New oral options on the way

- Semaglutide 50mg

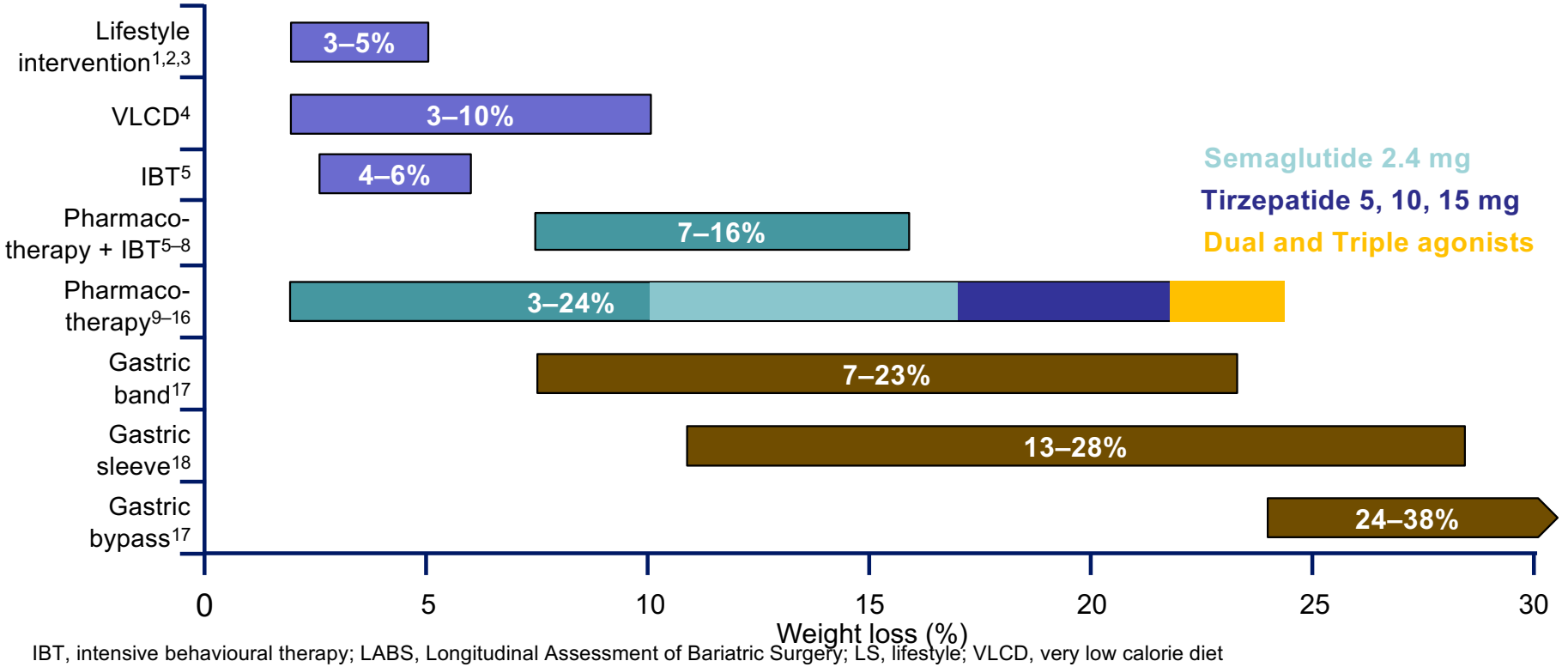


- Orforglipron (oral triple agonist)



- Knop et al Lancet 2023; Wharton et al NEJM 2023

Pharmacotherapy combined with lifestyle intervention can provide 17–24% weight loss; newer drugs are close to surgical efficacy



IBT, intensive behavioural therapy; LABS, Longitudinal Assessment of Bariatric Surgery; LS, lifestyle; VLCD, very low calorie diet

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Summary and Conclusions

- MASLD is an obesity-related disease, with multiple associated complications / co-morbidities, including T2DM and CVD
- Pharmacotherapy and bariatric surgery are both effective adjuncts to lifestyle modification and should be adopted more widely in the management of MASLD, especially as their benefits for other complications become clear
- Interventions are more likely to be effective if given at an early stage; they are less likely to work in established cirrhosis
- Newer agents with greater potency for weight loss are being developed; these may eventually prove effective for prevention and treatment of MASLD

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